Bristol Myers Squibb™

DASATINIB

RISK MANAGEMENT PLAN

Version Number: 17.0

Data-Lock Point for this RMP: 27-Jun-2021

Date of Final Sign-off: 15-Dec-2021

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EU RISK MANAGEMENT PLAN (RMP) FOR DASATINIB

RMP version to be assessed as part of this application:

Version Number: 17.0

Data-lock Point for this RMP: 27-Jun-2021

Date of Final Sign-off: 15-Dec-2021

Rationale for submitting an updated RMP:

- To reflect the reclassification of Nephrotic Syndrome from an important potential risk to an important identified risk
- To reflect the addition of Thrombotic Microangiopathy (TMA) as an important identified risk in alignment with the PSUR
- Updated with most recently available post-authorisation exposure data
- Updated information on the important potential risk of Severe Hepatotoxicities

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part II Safety Specification		
SI Epidemiology of the indication(s) and target population(s)	N/A	Version 16.1/ 06-Feb-2019
SII Non-clinical part of the safety specification	N/A	Version 16.1/ 06-Feb-2019
SIII Clinical trial exposure	N/A	Version 16.1/ 06-Feb-2019
SIV Populations not studied in clinical trials	N/A	Version 16.1/ 06-Feb-2019
SV Post-authorisation experience	Updated with most recently available post-authorisation exposure data	Version 17.0 / pending
SVI Additional EU requirements for the safety specification	N/A	Version 16.1/ 06-Feb-2019
SVII Identified and potential risks	N/A	Version 16.1/pending
SVIII Summary of the safety concerns	N/A	Version 16.1/pending
Part III Pharmacovigilance Plan	Updated to reflect Nephrotic Syndrome and Thrombotic Microangiopathy as important identified risks.	Version 17.0 / pending
Part IV Plan for post-authorisation efficacy studies	N/A	Version 13/22-Jan-2015

Summary of Significant Changes in this RMP

Part/Module	Summary of Major Changes	Version # / Date of Positive Opinion for Module Update
Part V Risk Minimisation Measures	Updated to reflect Nephrotic Syndrome and Thrombotic Microangiopathy as important identified risks.	Version 17.0 / pending
Part VI Summary of the Risk Management Plan	Aligned with proposed changes in current RMP	Version 17.0 / pending
Part VII Annexes		
ANNEX 2 Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	N/A	Version 16.1/ 06-Feb-2019
ANNEX 3 Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan	N/A	Version 16.1/ 06-Feb-2019
ANNEX 4 Specific adverse drug reaction follow-up forms	N/A	Version 16.1/ 06-Feb-2019
ANNEX 5 Protocols for proposed and on-going studies in RMP Part IV	N/A	Version 16.1/ 06-Feb-2019
ANNEX 6 Details of proposed additional risk minimisation activities	N/A	Version 16.1/ 06-Feb-2019
ANNEX 7 Other supporting data	N/A	Version 16.1/ 06-Feb-2019
ANNEX 8 Summary of changes to the risk management plan over time	Updated to include v17.0	Version 17.0 / pending

Other RMP versions under evaluation:

RMP Version Number	Submitted on	Procedure Number
None		

Details of the currently approved RMP:

Version number: 16.1

Approved with procedure: EMEA/H/C/000709/II/0059

Date of approval (opinion date): 06-Feb-2019

EU RMP Contact Person: Priv. Doz. Dr. Stefan Kaehler

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

1 PART 1: PRODUCT OVERVIEW

Table 1-1:	Product Details
Active substance(s) (INN or common name)	Dasatinib (as monohydrate)
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE06
Marketing Authorisation	Bristol-Myers Squibb Pharma EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	SPRYCEL®
Marketing authorisation procedure	Centralised
Brief description of the product	Dasatinib (SPRYCEL) inhibits the activity of the BCR-ABL kinase and SRC family kinases along with a number of other selected oncogenic kinases including c-KIT, EPH receptor kinases, and PDGFR-β receptor. SPRYCEL is a potent, subnanomolar inhibitor of the BCR-ABL kinase with potency at concentration of 0.60 0.8 nanomolar. It binds to both the inactive and active conformations of the BCR-ABL enzyme.
Hyperlink to the Product Information	Refer to proposed Product Information (PI)
Indication(s) in the EEA	**Current:** SPRYCEL is indicated for the treatment of adult patients with: ▪ newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase ▪ chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib ▪ Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy SPRYCEL is indicated for the treatment of paediatric patients with: ▪ newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib **Proposed:** SPRYCEL is indicated for the treatment of paediatric patients with: ▪ newly diagnosed Ph+ ALL in combination with chemotherapy

Table 1-1: Product Details

Dosage in the EEA

Current:

Adult Patients:

The recommended starting dosage of SPRYCEL for CP CML is 100 mg administered orally QD.

The recommended starting dosage of SPRYCEL for AP CML, myeloid or lymphoid BP CML, or Ph+ ALL is 140 mg, administered orally QD.

Paediatric Patients with Ph+ CML-CP

Dosing for children and adolescents is on the basis of body weight. Dasatinib is administered orally once daily in the form of either SPRYCEL film-coated tablets or SPRYCEL powder for oral suspension. The dose should be recalculated every 3 months based on changes in body weight, or more often if necessary. The tablet is not recommended for patients weighing less than 10 kg; the powder for oral suspension should be used for these patients. Dose increase or reduction is recommended based on individual patient response and tolerability. There is no experience with SPRYCEL treatment in children under 1 year of age.

SPRYCEL must be administered orally.
The film-coated tablets must not be crushed, cut or chewed in order to maintain dosing consistency and minimise the risk of dermal exposure; they must be swallowed whole. Film-coated tablets should not be dispersed as the exposure in patients receiving a dispersed tablet is lower than in those swallowing a whole tablet. SPRYCEL powder for oral suspension is also available for paediatric Ph+ CML-CP and Ph+ ALL patients, and adult CML-CP patients, who cannot swallow tablets.

SPRYCEL can be taken with or without a meal and should be taken consistently either in the morning or in the evening. SPRYCEL should not be taken with grapefruit or grapefruit juice

SPRYCEL film coated tablets and SPRYCEL powder for oral suspension are not bioequivalent. Patients who are able to swallow tablets and who desire to switch from SPRYCEL powder for oral suspension to SPRYCEL tablets or patients who are not able to swallow tablets and who desire to switch from tablets to oral suspension, may do so, provided that the correct dosing recommendations for the dosage form are followed.

Dosage of SPRYCEL powder for oral Suspension for patients with Ph+ CML-CP (10 mg/mL suspension upon constitution)

Body weight (kg)	Daily dose, mL (mg)
5 to less than 10 kg	4 mL (40 mg)
10 to less than 20 kg	6 mL (60 mg)
20 to less than 30 kg	9 mL (90 mg)
30 to less than 45 kg	10.5 mL (105 mg)
at least 45 kg	12 mL (120 mg)

The dose for the use of powder for oral suspension in adults patients with accelerated, myeloid or lymphoid blast phase (advanced phase) CML or Ph+ ALL has not been determined.

Table 1-1: Product Details

The recommended starting daily dosage of SPRYCEL tablets in paediatric patients is shown in the following table.

Dosage of SPRYCEL tablets for paediatric patients with Ph+ CML-CP

Body weight (kg)[a]	Daily dose (mg)
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

a The tablet is not recommended for patients weighing less than 10 kg; the powder for oral suspension should be used for these patients.

The recommended starting daily dosage of SPRYCEL powder for oral suspension for paediatric patients with Ph+ CML-CP and adult patients with Ph+ CML-CP who cannot swallow tablets is shown in the following table.

Table 1-1: Product Details

Proposed:

Paediatric population with Ph+ ALL

Dosing for children and adolescents is on the basis of body weight. Dasatinib is administered orally once daily in the form of either SPRYCEL film-coated tablets or SPRYCEL powder for oral suspension. The dose should be recalculated every 3 months based on changes in body weight, or more often if necessary. The tablet is not recommended for patients weighing less than 10 kg; the powder for oral suspension should be used for these patients. Dose increase or reduction is recommended based on individual patient response and tolerability. There is no experience with SPRYCEL treatment in children under 1 year of age.

The recommended starting daily dosage of SPRYCEL tablets in paediatric patients is shown in the following table:

Dosage of SPRYCEL tablets for paediatric patients with Ph+ ALL

Body Weight (kg)[a]	Daily Dose (mg)
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

[a] The tablet is not recommended for patients weighing less than 10 kg.

The recommended starting daily dosage of SPRYCEL powder for oral suspension for paediatric patients with Ph+ ALL and adult patients with Ph+ CML-CP who cannot swallow tablets is shown in the following table.

Dosage of SPRYCEL powder for oral Suspension for patients with Ph+ ALL (10 mg/mL suspension upon constitution)

Body weight (kg)	Daily dose, mL (mg)
5 to less than 10 kg	4 mL (40 mg)
10 to less than 20 kg	6 mL (60 mg)
20 to less than 30 kg	9 mL (90 mg)
30 to less than 45 kg	10.5 mL (105 mg)
at least 45 kg	12 mL (120 mg)

In clinical studies, treatment with SPRYCEL in paediatric patients with Ph+ ALL was administered continuously, added to successive blocks of backbone chemotherapy, for a maximum duration of two years. In patients that receive a subsequent stem cell transplantation, SPRYCEL can be administered for an additional year post-transplantation.

Pharmaceutical form (s) and strength(s)

Film-coated tablets: 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, 140 mg

Powder for oral suspension: 10 mg/mL

Table 1-1:	Product Details
Is/will the product be subject to additional monitoring in the EU?	No

2 PART II: SAFETY SPECIFICATION

2.1 Epidemiology of the Indication(s) and Target Population(s)

Indication

Dasatinib is an oral oncology agent.

It is indicated for the treatment of adults with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (CML) in chronic phase (CP) and adults with chronic, accelerated (AP), or blast-phase (BP) CML with resistance or intolerance to prior therapy including imatinib. It is also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

Dasatinib is indicated for the treatment of paediatric patients with newly diagnosed Ph+ CML in CP, or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib and for the treatment of paediatric patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) in combination with chemotherapy.

CML is a clonal myeloproliferative disorder resulting from a characteristic mutation (Ph+) in a pluripotent haematopoietic stem cell. The clinical course of CML is characterised by progression from an asymptomatic or mildly symptomatic CP lasting 3 to 6 years followed by transformation to AP and then BP (also referred to as blast crisis) of much shorter duration. Eventually, all untreated patients enter the terminal phase, which is characterised by rapidly rising white blood cell counts, susceptibility to life-threatening infections, and death within 3 to 6 months. CML is a rare disease, but is one of the more common forms of leukaemia in adults. It can occur at any age. The epidemiologic characteristics of CML are provided in Table 2.1-1.

ALL is also a clonal myeloproliferative disorder resulting from mutations in the haematopoietic stem cell. Ph+ ALL is a more aggressive leukaemia than ALL (without Ph+ mutation) and CML. Adult patients with Ph+ ALL historically have had a poor prognosis with low rates of overall survival (OS) and limited options for therapeutic intervention. ALL is the most common form of leukaemia in children, but can also occur at any age. The epidemiologic characteristics of ALL are presented in Table 2.1-2.

Table 2.1-1: Epidemiologic Characteristics of Chronic Myeloid Leukaemia (CML)

CML	
Incidence	The worldwide annual incidence of CML is estimated to be 1.2 cases per 100,000 among men and 0.7 per 100,000 among women.[1] An estimated 62,130 new cases of adult and childhood leukaemia have been diagnosed in the US in 2017; of these, CML will account for 8950 cases[2 3] Approximately 80% of patients with CML are diagnosed in the CP[4]. Population-based registries and studies report the following incidence rates, standardised to the world population[5,6]: US: 1.0 per 100,000; France: 0.8 per 100,000; Sweden: 0.7 per 100,000; United Kingdom (UK): 0.6 to 0.8 per 100,000; and Germany: 0.7 to 1.3 per 100,000. Among children and adolescents, CML is considered an even rarer disease. Age-adjusted incidence rates are as follows[7]: Ages <5 years: 1.1 per million; Ages 5 to 9: 0.7 per million; Ages 10 to 14: 1.1 per million; and Ages 15 to 19: 2.2 per million
Prevalence	In the US, an estimated 70,000 people were living with CML in 2010[8]. In Europe, prevalence estimates varied from 6.6 to 13.9 cases per 100,000 people. Specific estimates per 100,000 people are as follows: 4.5 in Lithuania[9]; up to 13.0 in Denmark[10] ; 10.8[11] in Italy; up to 9 in Finland[10]; 11.9 in Sweden.[12] Approximately fifteen percent of all adult leukaemias are CML.[13] CML among children is rare with approximately 2.5% of CML patients under the age of 20 years[14].
Demographics of the population: age, gender, racial and/or ethnic origin	CML can occur at all ages, although it is rarely seen in children below the age of 15[15], and the incidence increases exponentially with age[16]. About a third of patients with CML are over 60 years of age[17]. Surveillance, Epidemiology, and End Results (SEER, US) and Medical Research Council (MRC, UK), data report the median age of patients with CML to be 67 years. However, most patients in clinical trials are 50-60 years old (median 53 years)[14]. Patients from low and middle income countries are reported to be younger, with a median age of 37.8 years[18]. CML is more common in men than women with male -to-female ratios ranging between 1.3:1 and 1.8:1.[5, 19]. With regards to race, Caucasians have a greater incidence rate of CML than either blacks (rate ratio 1.22) or Hispanics (rate ratio 1.42) in the US[20]
Risk factors for the disease	Studies examining risk factors found an increased risk of CML with exposure to ionizing radiation[21] and benzene[22], and with increased body mass index (BMI)[23],

Table 2.1-1: Epidemiologic Characteristics of Chronic Myeloid Leukaemia (CML)

CML	
	[24]. Associations between the risk of CML and familial, geographic, ethnic, economic, or infectious agents have not been established [13]. Information on risk factors for CML in children is more limited. Down syndrome has been shown to be strongly associated with the risk for myeloid leukaemia. Other potential risk factors include maternal age <20 years, hypertension, Cesarean section delivery, maternal smoking and being one of a multiple birth.[25]
Main treatment options	There are several commercially available tyrosine kinase inhibitors (TKIs) for the treatment of CML including dasatinib, imatinib, nilotinib, ponatinib, bosutinib, and rodatinib (South Korea only) although only dasatinib, imatinib and nilotinib are indicated as first line treatment in CP CML. Dasatinib, imatinib, and nilotinib are approved for use in paediatric patients.
Mortality and morbidity (natural history)	The annual mortality rate has decreased worldwide from 10% to 1-2% since the implementation of TKI therapies.[26] Mortality rates increase with advancing age[27, 28]. The median survival observed in a US based study is 8.9 years for patients in CP, 4.8 years for patients in AP, and 6 months for patients in BP[28]. The median age at time of death in the US is 76; 0.6% of all CML deaths are in those less than 20 years of age.[29] While the incidence of CML has remained stable, the decreasing mortality and increasing duration of survival will increase disease prevalence in the years to come. It is estimated that by 2050, the prevalence rate will be 35 to 40 times the annual incidence of CML[8].
Important co-morbidities	Co-morbidities associated with the target population include myelosuppression, thrombosis, haemorrhage, and pleural effusion. <u>Myelosuppression</u> Limited population-based data evaluating the incidence of myelosuppression in CML patients is available, in particular the background incidence in untreated patients. Myelosuppression has been reported to occur in up to 50% of patients with CP CML treated with TKI inhibitors[30, 31, 32]. Higher rates of myelosuppression have been observed among patients receiving 2nd-line treatment for CP CML or those exposed to higher doses of imatinib in either 1st- or 2nd-line settings. [30,33,34] In an observational study of primarily patients with 1st-line CP CML in different treatment settings conducted in The Netherlands, Grade 3/4 myelosuppression was reported as 27.3% for thrombocytopaenia, 25.3% for neutropaenia, 5.5% for anaemia, and 4.4% for febrile neutropaenia[35]. In the clinical trial setting, the incidence of Grade 3/4 myelosuppression for CP CML patients treated with imatinib 1st-line setting was 3.1% to 10% for anaemia, 14% to 26% for neutropaenia and 7.8% to 25% for thrombocytopaenia[32,33,36,37]. From patients in 1st-line nilotinib clinical trial (n=61), the rates of All Grades haematologic toxicities were 52% for neutropaenia, 49% for anaemia, and 43% for thrombocytopaenia. Grade 3/4 event rates were 12% neutropaenia, 5% anaemia, and 11% thrombocytopaenia. [38]

Table 2.1-1: Epidemiologic Characteristics of Chronic Myeloid Leukaemia (CML)

CML	
	By phase, the incidence observed in clinical trials are as follows: Grade 3/4 neutropaenia: 35% imatinib CP patients with CML previously treated with interferon (IFN)-α, 13% newly diagnosed patients with CML receiving imatinib, 58% imatinib-treated advanced phase CML, 64% imatinib-treated myeloid blast crisis patients.[39] Grade 3/4 thrombocytopaenia: 20% imatinib-treated CP patients with CML previously treated with IFN-α, 8% newly diagnosed patients with CML receiving imatinib, 43% imatinib-treated advanced phase CML, 62% imatinib-treated myeloid blast crisis patients.[40] No population-based epidemiology studies have evaluated the incidence of myelosuppression among paediatric CML patients. Within a clinical trial of paediatric CML patients in late chronic and advanced phase, the rates of Grade 3/4 haematologic toxicities were less frequent among imatinib treated patients than previously reported rates in advanced phase adult CML patients. [41] Thrombosis Thromboses are known complications in patients with CML, as well as in other chronic myeloproliferative disorders and haematological malignancies. [42] A retrospective analysis of 115 patients observed thrombotic events in 6% of patients. Thrombotic events were increased in patients aged 70 and above, and were less frequent in patients below the age of 40, and after therapy with alkylating agents. No patients under the age of 20 had a thrombotic event. [42] Haemorrhage Population based estimates of incidence have not been reported in the published literature. A study that reviewed medical charts to study subdural haematomas among patients with CML treated with imatinib, observed an incidence of 5.8%. The median age of patients with subdural haematomas was 65 years of age and median duration of treatment was 10 weeks. All patients with haematomas had advanced disease and were initially treated at a dose of 600 mg/day of imatinib.[43] In the general population, the incidence of subdural haematomas is estimated to be between 1.0-15.0 patients per 100,000 people.[44] The overall incidence of upper gastrointestinal (GI) bleeding is approximately 100 hospitalisations per 100,000 adults per year with 10% mortality.[45] In a study including 63 patients with CML in which episodes of overt GI haemorrhage were evaluated, 10 (15.9%) patients with CML suffered an upper GI bleed while only one patient (1.6%) in BP had a lower GI bleed. GI bleeds was reported in 5 out of 19 (26.3%) patients with CML that had blastic transformation.[44]Although thrombocytopaenia was associated with several of the GI bleeds, 24% with upper GI bleed had platelet counts greater than 100,000 cubic millimetre (mm^3). A population-based study utilizing de-identified medical and pharmacy claims found that GI bleeding was reported in 1.7% of 357 patients with CML who were <65 years of age.[41]

Table 2.1-1: Epidemiologic Characteristics of Chronic Myeloid Leukaemia (CML)

CML	
	Kessler et al conducted a retrospective study that examined uncontrolled thrombocytosis associated with chronic myeloproliferative disorder.[46] There were only 4 patients with CML included in this study, but out of these 4 patients with CML, 1 had a GI bleed. In this study, (overall) bleeding was reported twice as frequently in patients over 59 years of age than in younger patients and no bleeding events was reported in those less than 51 one years of age.[45] No population-based studies of the incidence of haemorrhage among paediatric patients with CML were identified in the literature. Pleural Effusion Pleural effusion develops in approximately 3000 per million people per year. [47] Pleural effusions are common during the hospitalization of patients with haematologic malignancies.[48] Fluid overload, cardiac dysfunction and hypoalbuminaemia are a concern in this population. Among patients with CML treated with imatinib, fluid retention/oedema is one of the most common toxicities occurring in more than 50% of patients.[49] Pleural effusions are rarely diagnosed during the lifetime of patients with acute leukaemia (ALL, acute myelogenous leukaemia [AML]) but are a common finding by autopsy after death.[50] No population-based studies were identified in the literature that specifically evaluated or reported the incidence of malignant pleural effusion among adults or children with CML.

Table 2.1-2: Epidemiologic Characteristics of Acute Lymphoblastic Leukaemia (ALL)

ALL	
Incidence	An estimated 62,130 new cases of leukaemia has been diagnosed in the US in 2017; of these, ALL will account for 5970 cases.[51] The incidence of ALL decreases with age and ranges from 9-10 cases per 100,000 person-years in childhood to 1-2 cases per 100,000 person-years in US adults[52]. Incidence rates of ALL: Sweden: 0.5-1 case per 100,000 [53]; Brazil: 3.5 per 100,000 [54]; England: 0.5 - 0.6 per 100,000 [55,6] ; and Norway: 0.5 per 100,000 [56]. About 20-40% of adults with ALL have a mutation called the Philadelphia chromosome (Ph+). Only 3-5% of children have this same mutation.[53,54]
Prevalence	In the US, an estimated 69,567 people are living with ALL.[4] In Europe prevalence estimates varied from 8.3[9] to 30 cases per 100,000. Specific estimates per 100,000

Table 2.1-2: Epidemiologic Characteristics of Acute Lymphoblastic Leukaemia (ALL)

ALL	
	people are as follows: 8.3 per 100,000 in Lithuania[9], up to 26 in Denmark[10], up to 27 in Finland[10], and 30 in Italy[57].
Demographics of the population: age, gender, racial and/or ethnic origin	ALL can occur in all ages and is the most common form of leukaemia in children.[4, 23,58]. It is more common in males than females (IRR 2.2)[58]. The incidence of ALL is higher among Caucasians than other races in the US and Brazil[23,54,58].
Risk factors for the disease	Risk factors associated with developing ALL include prior chemotherapy for another cancer, exposure to high levels of radiation, certain genetic disorders (ie, Down's syndrome), and family history (sibling). A possible association with benzene has also been reported[59].
Main treatment options	Treatment options for ALL are based on disease characteristics and risk profile, and may include chemotherapy (induction, intensified consolidation, maintenance phases and central nervous system [CNS] prophylaxis). For Ph+ ALL TKIs may be added to optimize treatment. Allogeneic stem-cell transplantation is another approach for high-risk patients in first remission[60].
Mortality and morbidity (natural history)	Advances in ALL therapy have led to long-term survival >80% in children. However, only 30–40% of adults achieve long-term disease-free survival.[61] The age-adjusted mortality rate for 2006-2010 was 0.5 per 100,000 persons per year in the US.[27] In 2013, 1430 deaths due to ALL are expected to occur.[4] The overall 5-year relative survival for 2008-20014 in the US was 68.1%.[62] The relative 5-year survival is higher among children at 91%.[4] In the UK, the overall 5-year survival was reported as 69% UK.[63] Adults with Ph+ ALL have a poorer prognosis, with 10% surviving more than 1year.[64]
Important co-morbidities	Co-morbidities associated with the target population include myelosuppression, thrombosis, haemorrhage, and pleural effusion. <u>Myelosuppression</u> Myelosuppression is intrinsically a clinical baseline characteristic of ALL and therefore part of its definition. All ALL patients are myelosuppressed at some level at diagnoses, even if white cell counts may be normal, they are not functional. No studies were identified that reported the background incidence of myelosuppression in an untreated population of ALL patients. In imatinib and dasatinib treated patients the frequency of thrombocytopenia was 92% and 88% respectively.[65,66] <u>Thrombosis</u> A few population-based studies evaluating the incidence of thrombosis in ALL patients are available. In a population-based study in the United States of over 2,400 ALL patients the cumulative incidence of venous thromboembolism over 2 years was 4.5%. [67] In a cohort of 185 ALL patients prior to chemotherapy the incidence of thrombosis was 2.2%. [68] In two cohort studies of leukaemia patients in Italy the incidence of thrombosis among ALL patients was 4.7% and 10.6%. [69, 70] In a German cohort of 108 patients treated at a single institution, 13% experienced a thrombosis event. [71] A retrospective observational study of thromboprophylaxis

Table 2.1-2: Epidemiologic Characteristics of Acute Lymphoblastic Leukaemia (ALL)

ALL	
	among ALL in Dutch patients reported the incidence of thrombosis to be 8.5%.[72] Another study of 299 ALL patients treated at MD Anderson reported an incidence of venous thromboembolism of 17.7%.[73] In a study of ALL paediatric patients treated with asparaginase, 3.8% has an outcome of CNS thrombosis.[74] Haemorrhage No studies were identified that reported the background incidence of haemorrhage in an untreated population of ALL patients. The incidence of Grade 3 or 4 haemorrhage was 6%[75,76] to 12%[77] during treatment for ALL. The incidence of all grade haemorrhage was 15% in a dasatinib treated population.[76] Pleural Effusion Pleural effusions are rarely diagnosed during the lifetime of patients with acute leukaemia (ALL, acute myelogenous leukaemia [AML]) but are a common finding by autopsy after death.[50]

2.2 Nonclinical Part of the Safety Specification

The nonclinical safety profile of dasatinib was characterised in a drug-safety program including in vitro and in vivo studies in monkeys, dogs, rats, rabbits and mice. The nonclinical study results showed general relevance to clinical findings in key safety risks of myelosuppression, bleeding related events, QT prolongation, pulmonary toxicity and cardiotoxicity, embryo-fetal toxicity, as well as their dose relationship and, where pertinent, resolution with dose interruption, dose modification or treatment cessation.

At present, nonclinical findings of reproductive and developmental toxicity, carcinogenicity, phototoxicity and drug interactions remain potential clinical risks (not refuted by clinical data, and which are of unknown clinical relevance).

Overall, based on the intended use of dasatinib in patients with CML or Ph+ ALL, the scope and results of nonclinical pharmacology, PK, and drug safety evaluation programs support a positive benefit-risk assessment and the long-term oral administration of dasatinib in these patient populations.

Safety specifications for nonclinical findings are summarized in Table 2.2-1. A summary of preclinical safety is provided in Appendix 2.

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings	Relevance to human usage
Myelosuppression Following single or repeated oral doses of dasatinib, bone marrow toxicity was a consistent finding in rats and was accompanied by decreases in erythrocyte,	Dasatinib treatment may result in

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings	Relevance to human usage
lymphocyte, and platelet counts. In monkeys, minimal bone-marrow toxicity was reported in a small number of animals following repeat dosing, and was generally accompanied by decreases in erythrocyte and lymphocyte counts. Bone-marrow toxicity in animals was reversible following interruption of drug treatment.	myelosuppression and bleeding events in humans.
QT Prolongation	
Dasatinib activity in vitro in human ether a-go-go-related gene (hERG)/potassium channel rapid decayed rectifier and Purkinje fiber assays suggested a potential for prolongation of cardiac ventricular repolarisation (QT).[78] Dasatinib inhibited hERG currents by 6.1±1.2%, 36.5±6.3%, and 76.8±4.5% (n = 3) at 3, 10, and 30 micromolar (μM), respectively. The calculated IC50 was 14.3 μM, which is approximately 150-fold greater than the plasma Cmax measured in humans at clinically relevant doses. Dasatinib prolonged Action Potential Duration (APD50) by 26 ± 5% and APD90 by 11 ± 0% in Purkinje fibers at 30 μM. Dasatinib at a single oral dose of 10 mg/kilogram (kg) in conscious, unrestrained monkeys elicited no drug-related changes in electrocardiogram (ECG) parameters, including in QT Interval. .[36]	Dasatinib treatment may result in QT prolongation in humans.
Reproductive and Developmental Toxicity	
Dasatinib did not affect male or female fertility in a conventional rat fertility and early embryonic development study, but induced embryolethality at dose levels approximating human clinical exposures. In embryofoetal development studies, dasatinib likewise induced embryolethality with associated decreases in litter size in rats, as well as foetal skeletal alterations in both rats and rabbits. These effects occurred at doses that did not produce maternal toxicity, indicating that dasatinib is a selective reproductive toxicant from implantation through the completion of organogenesis.[79, 80, 81]	Dasatinib treatment may result in foetal/neonatal toxicity (including malformations) in humans.
The embryo-foetal developmental toxicity profiles of dasatinib and imatinib were compared. Both dasatinib and imatinib, when administered during the period of organogenesis, decreased litter size and induced embryo lethality, and foetal skeletal abnormalities in rats. Dasatinib also induced foetal skeletal abnormalities in rabbits, whereas no evidence of foetal abnormalities was observed with imatinib in the rabbit. A preliminary range-finding study[82] in rats confirmed that dasatinib administration causes extensive developmental mortality at doses associated with sub-therapeutic clinical exposures. Therefore, a definitive pre- and postnatal development study of dasatinib in rats for dasatinib is not feasible and would not provide any additional relevant clinical information.	Dasatinib use during pregnancy or nursing may result in foetal or infant toxicity

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings	Relevance to human usage
In an oral range-finding study of peri- and postnatal development in rats,[82] dasatinib (5 and 10 mg/kg/day) was given to female rats in 3 cohorts with dosing initiated on gestational day (GD) 16 (the end of organogenesis), GD 21 (the approximate onset of parturition), or lactation day (LD) 4 with continuation of dosing up to LD 20. At ≥ 5 mg/kg/day (area under the curve (AUC)[0-8h]): 144 ng•h/mL; ≥ 0.4×), adverse maternal clinical observations were associated with reduced body weights (≤ 8%, from GD 21 to end of dosing) and food consumption, abnormal parturition and dehydration, perivaginal discharge, soiling, red-stained haircoat, unkempt appearance, and reduced/absent post-parturitional grooming. Gross necropsy observations in dams were limited to small spleen in 3 dams at ≥ 5 mg/kg/day. In the pups in all cohorts, exposure to dasatinib was associated with white fluid-filled thoracic cavities (chylothorax). Among dosing cohorts pup necropsy findings at ≥ 5 mg/kg/day consisted of fluid-filled thoracic cavity in 20/47 (GD 16; 5 mg/kg/day), 16/42 (GD 21; 5 mg/kg/day) and 30/30 (GD 21; 10 mg/kg/day) of the pups examined. Maternal treatment with dasatinib beginning on LD 4 also resulted in labored respiration in the pups, which correlated with the finding of white fluid-filled thoracic cavities at necropsy (found in 25/57 pups evaluated). Thus, indirect *(in utero)* exposure (≥5 mg/kg/day) of pups to dasatinib from the end of organogenesis through LD 4 was associated with pleural effusion at sub-therapeutic maternal exposures (AUC: 144 ng•h/mL; 0.4×).	Dasatinib exposure *in utero* or through lactation in rats leads to pleural effusion and lethality in pups even at sub therapeutic maternal exposure.
Pulmonary Toxicity including Pleural Effusion Review of the nonclinical toxicology studies reveal that no pulmonary effects were observed in monkeys, in a single dose (10 mg/kg) cardiovascular safety pharmacology study[83] or when dosed with dasatinib up to 9 months[84] at doses up to 4.5 mg/kg/day (261 ng•h/mL; 0.7×). However, changes likely due to altered pulmonary haemodynamics were noted in 2 studies in rats: 1) 6-month oral toxicity study; and 2) an oral range finding study of peri- and post natal development. In the 6-month oral toxicity study in rats,[85] the high dose of 15 mg/kg/day was reduced to 10 mg/kg/day in Week 8 and to 8 mg/kg/day in Week 17 due to GI toxicity. Nine (9) males and 2 females from the high-dose main study group (15/10/8 mg/kg/day) and 7 males from the high dose toxicokinetic group were found dead or sacrificed in a moribund condition before scheduled study termination between Days 23 and 160. In animals that died, clinical signs observed prior to death included substantial body weight loss, swollen abdomen, hunched posture, thin appearance, irregular respiration, faecal abnormalities (few, liquid, and nonformed), and red (faecal stained) or rough haircoat. There was accumulation of clear or red fluid in the thoracic cavity (consistent with pleural effusion with or without hemorrhage) in 6 of the 9 males and in both females. Six (6) of these rats also had minimal segmental medial arteriolar hyperplasia in the lungs, a change that typically is a response to sustained haemodynamic changes including increases in pressure and/or volume. The mean systemic exposure (AUC[0-24h]) on Week 26 (8 mg/kg/day) was 2.1× (664 ng•h/mL) the exposure (AUC[0-24h]) at the efficacious human dose of 100 mg once daily (QD) in CML patients (308 ng•h/mL). No pleural effusions or pulmonary vascular changes were seen at ≤4 mg/kg/day (370 ng•h/mL; 0.9×). There was no evidence of dasatinib-related pleural effusion or pulmonary morphologic changes administered up to 3 mg/kg/day in a 2-year oral	Dasatinib exposure in rats results in pleural effusions at exposures very similar (≥2×) to that achieved at human therapeutic exposure (100 mg QD). Pulmonary related side-effects in patients treated with dasatinib include pleural effusions and lung parenchymal changes such as ground glass or alveolar opacities and septal thickening as well as PAH. Lifetime exposure of rats to dasatinib at exposures equivalent to those in humans at the recommended high dose did not cause pleural effusions or pulmonary changes

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings	Relevance to human usage
carcinogenicity study in rats.[86] Systemic exposures at the high dose of 3 mg/kg/day were approximately equivalent (AUC 236 ng•h/mL; 0.6×) to the efficacious human exposure. In conclusion, data from the nonclinical studies indicate that chronic dasatinib treatment in rats but not in the monkeys resulted in pleural effusion and pulmonary vascular changes that likely were a consequence of altered pulmonary haemodynamics (ie, increased pressure) at systemic exposures greater than (≥ 2×) those achieved at therapeutic exposure (100 mg QD). Additionally, dasatinib exposure *in utero* through early lactation also resulted in pleural effusion in pups (but not dams) at sub-therapeutic maternal exposures (≤ 0.7×).	(based on histopathology).
Pulmonary Arterial Hypertension (PAH) The tyrosine kinase inhibitor (TKI) imatinib, indicated for chronic myelogenous leukaemia (CML) is being investigated as a potential treatment for PAH due to its anti-vasoproliferative-property. However, dasatinib has been associated with some cases of PAH in heavily pre-treated patients although the PAH does not appear to be classical, as partial or complete reversibility is seen after discontinuing dasatinib. Despite the differential kinase profile, intervention studies in rat models of experimental PAH suggested that the two TKIs are equally efficacious in reversing functional hemodynamic and structural proliferative changes. Therefore, nonclinical *in vivo* (SD rats) and *in vitro* (human pulmonary artery endothelial cells/smooth muscle cells [hPAEC/hPASM) studies evaluating effects of the two TKIs were conducted to understand potential mechanistic differences for the apparent differential clinical effect. Nonclinical *in vivo* (Sprague Dawley rats) and *in vitro* (human pulmonary artery endothelial cells (hPAEC)/human pulmonary artery smooth muscle cells (hPASM) studies evaluating direct effects of imatinib and dasatinib were conducted to understand the potential mechanistic differences for the apparently different clinical effect on PAH. The *in vivo* study explored effects of clinically relevant doses of imatinib and dasatinib (30 or 8 mg/kg/day, oral) and monocrotaline (single sub-cutaneous dose, 70 mg/kg; positive control) on PAH-related pulmonary changes in rats (1-month treatment). Monocrotaline reduced nitric oxide (NO; vasodilation) and increased endothelin (ET)-1; vasoconstriction) levels in plasma, induced structural changes (perivascular inflammation, endothelial cell injury and smooth muscle cell proliferation) in pulmonary artery (PA) and lungs, and increased (2-5× control) systolic and diastolic pulmonary arterial pressure (PAP) and right ventricular pressure. In contrast, both imatinib and dasatinib increased NO in plasma (3×), did not induce any PAH-related structural changes (PA or lungs) and did not alter haemodynamic function compared to vehicle control treated rats. The *in vitro* hPAEC/hPASM co-culture model demonstrated that both imatinib and dasatinib at clinically relevant (Cmax) concentrations increased NO and decreased ET-1 protein and mRNA. In conclusion, dasatinib, as imatinib, does not have the potential to directly induce PAH-related changes *in vivo* or *in vitro*. In addition, both molecules induce biochemical changes in vivo and in vitro consistent with a protective effect on PAP.[87] Clinical findings of dasatinib-related PAH have not been explained by non-clinical experiments to date.	The incidence of PAH is low in patients treated with dasatinib.
Carcinogenicity A 2-year oral carcinogenicity study in rats that included statistical analyses of data on combined neoplasms of similar cellular origin, indicated that dasatinib	The relevance of dasatinib treatment

Table 2.2-1: Summary of Significant Non-clinical Safety Findings

Key Safety Findings	Relevance to human usage
significantly increased the combined incidences of uterine squamous cell papillomas and carcinomas in high-dose females. Dasatinib also resulted in a statistically significant increased incidence of prostate adenomas in low-dose males when the intermediate- and high doses were excluded from the analysis. The highest dose resulted in a plasma drug exposure (AUC) level generally equivalent to human exposure at the recommended range of starting doses from 100 mg.	resulting in carcinogenicity in humans is unknown.
Cardiotoxicity The in vitro cardiotoxic potential of dasatinib as compared to imatinib, at pharmacologically-relevant concentrations, was investigated in primary rat cardiomyocytes. Dasatinib did not significantly affect mitochondrial membrane potential, cell viability, apoptosis, or cellular ultrastructure in vitro, whereas imatinib significantly affected these parameters. These results suggest that, unlike imatinib, at pharmacologically-relevant concentrations, dasatinib does not induce cardiotoxicity in vitro. An in vivo study in mice showed no functional or structural evidence that dasatinib induced cardiotoxicity at daily oral doses of up to 14 mg/kg/day (mean AUC≤ 1,260 ng•h/mL) for 1 month. This dose resulted in systemic exposures that were 3× higher than exposures in patients receiving a clinical dose of 100 mg QD. In addition, the study did not replicate the cardiotoxicity findings reported in mice receiving oral imatinib at daily doses of 200 mg/kg/day (mean AUC value of 40,500 ng•h/mL) for 1 month, a dose that resulted in exposures equivalent to those achieved in patients at the recommended imatinib clinical dose of 400 mg.[88] Therefore the in vivo study in mice did not reproduce the cardiotoxicity seen in the Kerkela study with imatinib.	Cardiac mitochondrial toxicity has not been observed in humans. Congestive heart failure (CHF) has been observed in humans in particular in patients with risk factors for CHF including previous imatinib therapy.
Phototoxicity Dasatinib had phototoxic potential in an in vitro neutral red uptake phototoxicity assay in mouse fibroblasts.[89] However, dasatinib was not phototoxic in vivo after a single oral administration to female hairless mice at exposures up to 3-fold the human exposure following administration of the recommended therapeutic dose (based on AUC).[90]	Dasatinib treatment is not likely to be phototoxic in humans.
Drug-Drug Interactions Dasatinib is a time-dependent inhibitor of cytochrome P450 enzyme (CYP) 3A4 (KI = 1.9 μM, kinact = 0.022 per minute). It is not an inducer of CYP3A4.[91,92] Dasatinib may decrease the metabolic clearance of drugs that are primarily metabolised by CYP3A4. Dasatinib is also a competitive inhibitor of CYP2C8 (Ki = 3.6 μM) and may therefore, decrease the metabolic clearance of drugs that are metabolised by CYP2C8.[81]	Dasatinib treatment may result in specific and limited drug interactions in humans.

2.2.1 Conclusions on Nonclinical Data

Table 2.2.1-1: Nonclinical Safety Concerns

Important Identified Risks (confirmed by clinical data)

Table 2.2.1-1: Nonclinical Safety Concerns

Myelosuppression	In humans, dasatinib treatment-related myelosuppression, manifested as thrombocytopaenia, neutropaenia, and anaemia are identified clinical safety risks. (see section 2.7.3)
Bleeding Related Events	In the clinical trial program, haemorrhage events have been reported in 7% (n=2440) subjects. Severe bleeding related events were most often associated with severe thrombocytopaenia.[93]
QT Prolongation	Dasatinib activity in vitro in hERG and Purkinje fiber assays (Cmax exposure margin 150x) does not suggest QT prolongation at clinically relevant exposure in humans. Therefore, QT prolongation is not expected in humans based on the nonclinical data. Of the 2440 adult patients with CML or Ph+ ALL treated with dasatinib in clinical studies, 15 patients (<1%) had corrected QT (QTc) prolongation reported as an adverse reaction (AR). No cases of torsades de pointes were identified amongst the 2440 pooled treated subjects across all indications.[94]
Pulmonary Toxicity	Pulmonary related side effects in patients treated with dasatinib include pleural effusions, pulmonary hypertension and pulmonary oedema, and lung infiltration and pneumonitis.
Reproductive and Developmental Toxicity	Dasatinib treatment may result in pregnancy-related malformative or foeto/neonatal toxicity in humans based on data in the corporate safety database
Pulmonary Arterial Hypertension	Pulmonary hypertension and PAH have been reported in the clinical setting.
Important Potential Risks (not refuted by clinical data or which are of unknown significance)	
Cardiotoxicity (Cardiac Adverse Reactions [ARs])	Dasatinib does not show cardiotoxic potential based on lack of mitochondrial toxicity in cardiomyocytes or structural and functional changes in non-clinical studies. Therefore, dasatinib is not expected to be cardiotoxic based on non-clinical studies. The cardiac ARs of congestive heart failure (CHF), cardiac dysfunction, myocardial infarction (MI), and cardiomyopathy have been reported in clinical studies. Post-marketing spontaneous reports of atrial fibrillation/atrial flutter have been reported in patients taking dasatinib.[81]
Carcinogenicity	The relevance of dasatinib treatment resulting in carcinogenicity in humans is unknown.
Phototoxicity	Based on the in vivo data in female hairless mice, dasatinib is not likely to be phototoxic in humans. Dasatinib treatment may have phototoxic potential in humans. In the clinical trial database phototoxicity has been reported uncommonly.[92]
CYP3A4 Drug Interactions	Dasatinib is a time-dependent inhibitor of cytochrome P450 enzyme (CYP) 3A4 but not an inducer. Dasatinib may decrease the metabolic clearance of drugs that are primarily metabolised by CYP3A4.
Missing Information	
Paediatric Patient Use	Juvenile animal safety studies have not been conducted.

2.3 Clinical Trial Exposure

Dasatinib has been studied in a comprehensive clinical development program in multiple Phase 1, 2, and 3 studies in adult and paediatric subjects with CML and Ph+ ALL. An overview of the dasatinib clinical program supporting the safe and effective use of dasatinib is in Table 2.3-1.

Table 2.3-1: Summary of Key Dasatinib Clinical Studies in CML and Ph+ ALL

Study	Study Design (Phase)	Number of Subjects Dosed Overall (dasatinib)/Study Status
Studies in Adult Subjects with CML and Ph+ ALL		
CA180002[95]	Phase 1 dose-escalation study of dasatinib: safety, PK, and PD in subjects with CP, AP, BP CML, or Ph+ ALL with resistance to imatinib	91 (91)/Completed
CA180005[96]	Phase 2 study of dasatinib in subjects with AP or CP CML resistant to or intolerant of imatinib	174 (174)/Completed
CA180006[97]	Phase 2 study of dasatinib in subjects with myeloid BP CML resistant to or intolerant of imatinib	109 (109)/Completed
CA180013[98]	Phase 2 study to determine activity of dasatinib in subjects with CP Ph+ CML resistant to high-dose imatinib or intolerant of imatinib	387 (387)/Completed
CA180015[99,100]	Phase 2 study of dasatinib in subjects with lymphoid BP CML or subjects with Ph+ ALL resistant to or intolerant of imatinib	94 (94)/Completed
CA180017[101]	Phase 2 randomized open-label study of dasatinib versus imatinib in subjects with CP Ph+ CML resistant to imatinib	150 (101)/Completed
CA180031[102]	Phase 1/2 study of dasatinib in subjects with CML and Ph+ ALL resistant to or intolerant of imatinib (Japan)	54 (54)/Completed
CA180034, [103, 104, 105, 106]	Phase 3 open-label dose-optimization study in subjects with CP CML who are resistant to or intolerant of imatinib	662 (662)/Completed
CA180035[107, 108, 109]	Phase 3 open-label dose-optimization study in subjects with AP CML, BP CML (myeloid and lymphoid), or Ph+ ALL resistant to or intolerant of imatinib	609 (609)/Completed
CA180036[110]	Phase 1/2 long-term safety and efficacy study in subjects with CML and Ph+ ALL who completed CA180031 (Japan)	54 (54)/Completed[a]
CA180039[111]	Long-term safety and efficacy study in subjects with CML or Ph+ ALL who experienced benefit on CA180002	46 (46)/Completed[a]
CA180043[112]	Phase 2B open-label study comparing dasatinib versus high-dose imatinib in subjects with CP CML with suboptimal response after 3 months of imatinib	32 (19)/Completed

Table 2.3-1: Summary of Key Dasatinib Clinical Studies in CML and Ph+ ALL

Study	Study Design (Phase)	Number of Subjects Dosed Overall (dasatinib)/Study Status
CA180056[113, 114, 115, 116]	Phase 3 open-label study comparing dasatinib versus imatinib in subjects with newly diagnosed CP CML	516 (258)/Completed
CA180138[117]	Phase 2 comparing dasatinib 50 mg BID or 100 mg QD in subjects with CP Ph+ CML resistant to or intolerant of imatinib (Japan)	23/ (23)Completed
CA180160[118]	Phase 2 study in Chinese subjects with CP/AP CML resistant to or intolerant of imatinib (China)	121 (121)/Ongoing
CA180188[119]	Phase 2 continuation study of dasatinib in subjects with CML or Ph+ ALL with clinical benefit on current SRC/ABL Tyrosine kinase inhibition Activity Research Trial (START) protocols	237 (223)/Completed
CA180363	Phase 2 open-label study in subjects with newly diagnosed CP Ph+ CML (initially designed with smoothened transmembrane protein [SMO] antagonist; enrollment terminated prior to initiation of randomized component)	66 (66)/ Completed
CA180399	Phase 2B open-label study comparing dasatinib versus imatinib in subjects with CP CML without an optimal response to 3 months of imatinib therapy	131 (90)/Ongoing
CA180400	Phase 4 open-label study of dasatinib in subjects with CP CML with chronic low-grade non-haematologic toxicity to imatinib	39 (39)/Ongoing
CA180406	Open-label single arm Phase 2 study evaluating dasatinib therapy discontinuation in patients with CP-CML with stable complete molecular response (CMR)	84 (84)/Ongoing
Combination Studies in Subjects with CML		
CA180323	Phase 1 open-label dasatinib/SMO combination study in subjects with CP or AP CML with resistance or suboptimal response to a prior TKI	27 (27)/Completed
CA180373	A Phase 1B Dose Escalation Study to Investigate the Safety, Tolerability and Preliminary Efficacy for the Combination of Dasatinib (BMS-354825) plus Nivolumab (BMS-936558) in Patients with Chronic Myeloid Leukaemia (CML)	27 (27) Ongoing
Studies in Paediatric Subjects with CML and Ph+ ALL		
CA180018[120, 121]	Phase 1 study of SRC/ABL TKI dasatinib in children and adolescents with relapsed or refractory leukaemia	58 (58)/Ongoing
CA180038[122, 123]	Phase 1 study of dasatinib in children with recurrent/refractory solid tumours or imatinib	40 (40)/Completed

Table 2.3-1: Summary of Key Dasatinib Clinical Studies in CML and Ph+ ALL

Study	Study Design (Phase)	Number of Subjects Dosed Overall (dasatinib)/Study Status
	resistant Ph+ leukaemia (investigator sponsored trial [IST])	
CA180204[124]	Phase 2 study to determine feasibility/toxicity of chemotherapy regimen + dasatinib for children with Ph+ ALL (IST)	62 (62)/Completed[b]
CA180226[125,]	Phase 2 study in children/adolescents with Ph+ leukaemia resistant to or intolerant of prior therapies including imatinib	130 (130)/Ongoing
CA180372	Phase 2 historically controlled study of dasatinib added to standard chemotherapy in paediatric subjects with newly diagnosed Ph+ ALL	106 (106)/Ongoing

Abbreviations: DLT = dose-limiting toxicity; IST= investigator sponsored trial, PK = Pharmacokinetics, PD = pharmacodynamics; SMO = smoothened transmembrane protein; START = SRC/ABL Tyrosine kinase inhibition Activity Research Trial, TKI = tyrosine kinase inhibitor

[a] Roll-over study. Figures do not count towards cumulative exposure; studies counted in an earlier study in this table.

[b] Cooperative group study, not counted toward cumulative dasatinib exposure

Pooled adult patient exposure data by duration, dose (if applicable), age group and gender, and ethnic or racial origin for pivotal clinical trials with dasatinib (CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180056, CA180160, CA180188, and CA180363) are presented in Table 2.3-2, Table 2.3-3, Table 2.3-4, and 2.3-5. Exposure tables are presented in Appendix 3.

Table 2.3-2: Duration of Exposure in Adult Population with CML and Ph+ ALL to Study Medication Up to Jun-2016 (Pooled Studies)

Total Exposed Adult Population		
Duration of exposure	**Patients N=2712**	**Persons Time (months)**
0 - 3 months	455	637
3 - 6 months	289	1268
6 - 9 months	204	1517
9 - 12 months	157	1638
12 - 18 months	215	3231
18 - 24 months	166	3507
24 - 30 months	232	6159
30 - 36 months	121	3993
36 - 48 months	162	6829

Table 2.3-2: Duration of Exposure in Adult Population with CML and Ph+ ALL to Study Medication Up to Jun-2016 (Pooled Studies)

Total Exposed Adult Population		
48 - 60 months	121	6645
60 - 72 months	258	16746
72 - 84 months	119	9372
84 - 96 months	163	14177
96 - 108 months	20	2093
108 - 120 months	26	2865
Total person time	**2712**	**80677**

Table 2.3-3: Clinical Exposure by Dose in Adult Population with CML and Ph+ ALL to Study Medication Up to Jun-2016 (Pooled Studies)

Total Adult Population		
Dose of exposure	**Patients N=2712**	**Persons Time (months)**
100 mg QD[a]	548	25436
140 mg QD	470	11404
50 mg BID[b]	178	7043
70 mg BID	1464	35720
Other	52	1586
Total	**2712**	**81189**

[a] once daily (QD)

[b] twice daily (BID)

Table 2.3-4: Clinical Exposure by Age Group and Gender in Adult Population with CML and Ph+ ALL to Study Medication Up to Jun-2016 (Pooled Studies)

Total Adult Population				
Age Group (years)	Patient N=2712s		Person time (months)	
	Male	Female	Male	Female
< 21	24	10	454	405
21 - 45	503	366	16870	12741
46 - 65	639	618	18841	19260
66 - 75	223	231	5270	5537
> 75	54	44	859	952
Total	**1443**	**1269**	**42299**	**38895**

Table 2.3-5: Clinical Exposure by Ethnic or Racial Origin in Adult Population with CML and Ph+ ALL to Study Medication Up to Jun-2016 (Pooled Studies)

Total Adult Population		
Ethnic/racial origin	Patients N=2712	Person time (months)
White	2042	57985
Black/African American	125	3254
Asian	442	16404
Other	91	3276
American Indian/ Alaska Native	1	40
Native Hawaiian/Other Pacific Islanders	1	0
Unavailable	10	229
Total	**2712**	**81188**

Paediatric patient exposure data by duration, dose (if applicable), age group and gender, and ethnic or racial origin for clinical trials CA180018 and CA180226 with dasatinib are presented in Table 2.3-6, Table 2.3-7, Table 2.3-8 and Table 2.3-9. Paediatric patient exposure in clinical trials with dasatinib added to chemo-therapy for studies CA180204 and CA180372 are presented in Table 2.3-10, Table 2.3-11, Table 2.3-12 and Table 2.3-13. Exposure tables are presented in Appendix 3.

Table 2.3-6: Duration of Exposure in Paediatric Patients with Ph+ CML-CP Studies CA180018 and CA180226, Dasatinib Mono-therapy (Totals)

Total Exposed Paediatric Population		
Duration of exposure	**Patients N=188**	**Persons Time (months)**
0 - 3 months	44	50
3 - 6 months	13	57
6 - 9 months	7	51
9 - 12 months	8	85
12 - 18 months	7	107
18 - 24 months	7	155
24 - 30 months	18	478
30 - 36 months	13	441
36 - 48 months	12	517
48 - 60 months	40	2156
60 - 72 months	8	526
72 - 84 months	8	608
84 - 96 months	2	177
96 - 108 months	1	100
Total person time	**188**	**5508**

Table 2.3-7: Clinical Exposure by Dose in Paediatric Patients with Ph+ CML-CP Studies CA180018 and CA180226 (Totals)

Total Paediatric Population		
Dose of exposure	**Patients N=188**	**Persons Time (months)**
60 mg/m^2	105	4147
80 mg/m^2	38	468
100 mg/m^2	6	8
120 mg/m^2	6	3
72 mg/m^2 (PFOS)[a]	33	882
Total	**188**	**5535**

[a] PFOS=powder for oral suspension; all other doses relate to tablet

Table 2.3-8: Clinical Exposure by Age Group and Gender in Paediatric Patients with Ph+ CML-CP Studies CA180018 and CA180226 (Totals)

Total Paediatric Population				
Age Group (years)	**Patients N=188**		**Person time (months)**	
	Male	**Female**	**Male**	**Female**
< 2	1	4	36	145
2 -11	50	37	1401	855
12 -17	54	39	1554	1416
> 17	0	3	0	100
Total	**105**	**83**	**2991**	**2516**

Table 2.3-9: Clinical Exposure by Ethnic or Racial Origin in Paediatric Patients with Ph+ CML-CP Studies CA180018 and CA180226 (Totals)

Total Paediatric Population		
Ethnic/racial origin	**Patients N=188**	**Person time (months)**
White	141	3884
Black/African American	7	169
Asian	35	1357
Other	4	42
American Indian/ Alaska Native	1	56
Total	**188**	**5508**

Table 2.3-10: Duration of Exposure in Paediatric Patients with Ph+ ALL Studies CA180204 and CA180372; Dasatinib added to Chemo-therapy (Totals)

Total Exposed Paediatric Population[a]		
Duration of exposure	**Patients N=161**	**Persons Time (months)**
0 - 3 months	15	2
3 - 6 months	12	50
6 - 12 months	13	85
12 - 24 months	80	1622
24 - 36 months	40	194
Total	**161**	**1953**

[a] Study CA180204[124] was a cooperative group study, not counted toward cumulative dasatinib exposure

Table 2.3-11: Clinical Exposure by Dose in Paediatric Patients with Ph+ ALL Studies CA180204 and CA180372; Dasatinib added to Chemo-therapy (Totals)

Total Paediatric Population[b]		
Dose of exposure	**Patients**	**Persons Time (months)**
60 mg/m^2	161	1953
Total	**161**	**1953**

[b] Study CA180204[124] was a cooperative group study, not counted toward cumulative dasatinib exposure

Table 2.3-12: Clinical Exposure by Age Group and Gender in Paediatric Patients with Ph+ ALL Studies CA180204 and CA180372; Dasatinib added to Chemo-therapy (Totals)

Total Paediatric Population[a]				
Age Group (years)	**Patients N=161**		**Person time (months)**	
	Male	**Female**	**Male**	**Female**
< 2	5	2	47	48
2 -11	59	44	681	600
12 -17	30	20	374	205
> 17	1	0	0	0
Total	**95**	**66**	**1102**	**853**

[a] Study CA180204[124] was a cooperative group study, not counted toward cumulative dasatinib exposure

Table 2.3-13: Clinical Exposure by Ethnic or Racial Origin in Paediatric Patients with Ph+ ALL Studies CA180204 and CA180372; Dasatinib added to Chemo-therapy (Totals)

Total Paediatric Population[a]		
Ethnic/racial origin	**Patients N=161**	**Person time (months)**
White	120	1504
Black/African American	20	212
Asian	6	75
Other	11	150
Native Hawaiian/Other Pacific Islander	2	2
American Indian/ Alaska Native	3	10
Total	**161**	**1953**

[a] Study CA180204[124] was a cooperative group study, not counted toward cumulative dasatinib exposure

2.4 Populations Not Studied in Clinical Trials

2.4.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Table 2.4.1-1: Important Exclusion Criteria in Pivotal Clinical Studies

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale (if not included as missing information)
Pregnancy or breast feeding women	True incidence of dasatinib-induced infant and foetal anomalies in male and female subjects difficult to determine	Yes	NA
Prior or concurrent malignancy	Limited data on risk	No	Potential effects of dasatinib on concurrent malignancy or malignancy induced by TKI may be difficult to identify. Long latency for the development of second tumours would be anticipated
Uncontrolled or significant cardiovascular disease (eg, MI within 6 months)	Suitability of dasatinib for patients with significant cardiovascular disease unknown	No	Direct cardiotoxic effects (eg, cardiomyopathy) is an important potential risk with use of dasatinib.
Patients currently taking drugs with a risk of causing torsades de pointes	Suitability of dasatinib for patients on drugs that may cause torsades de pointes is unknown	No	QT Prolongation is an important identified risk with use of dasatinib.
Bleeding disorders	Subjects excluded with history of significant bleeding disorder. Few studies allowed subjects on drugs that inhibit platelet function	No	Dasatinib causes thrombocytopaenia and has known effects on platelet function. Bleeding risk of dasatinib with concurrent bleeding/platelet disorder is unknown.
Hepatic dysfunction	Potential effects on subject safety and dasatinib exposure	No	Severe hepatotoxicities is an important potential risk with use of dasatinib.

2.4.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect rare and very rare adverse drug reactions including PAH and those that may occur with dasatinib exposure in patients at high risk of bleeding, patients with prior or concurrent malignancy, patients with uncontrolled or significant cardiovascular disease, patients with hepatic or renal dysfunction, or in patients < 1 year of age.

2.4.3 *Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes*

Table 2.4.3-1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Pregnant women	104 subjects[a]
Breastfeeding women There is no definitive information/on the excretion of dasatinib in human breast milk. However the physico-chemical and available pharmacodynamic (PD)/toxicological data on dasatinib point to excretion in human breast milk and a hence to a risk to the nursing child and therefore, women on dasatinib must not breast feed.	No clinical studies conducted
Patients with relevant comorbidities	
Patients with hepatic impairment [126]	Moderate: 8 subjects (0.24 person-months)[b] Severe: 5 subjects (0.15 person-months)[b]
Patients with renal impairment	No clinical studies conducted
Patients with cardiovascular impairment [127]	61 subjects (305 person-years)[c]
Immunocompromised patients Post- haematopoietic stem cell transplant (HSCT) for Ph+ leukaemias [128]	23 subjects (25.8 person-years)[d]
Bleeding risk or concomitant use of anti-platelet agents	No clinical studies conducted
Patients with a disease severity different from inclusion criteria in clinical trials:	No clinical studies conducted
Population with relevant different ethnic origin	No clinical studies conducted
Subpopulations carrying relevant genetic polymorphisms	No clinical studies conducted
Other	
Elderly[129,116]	≥65 years: 20 subjects (100 person-years)[e] 66-75 years: 309 subjects (386.5 person-years)[f] and >75 years: 53 subjects (66.3 person-years)[f]
Children[132,130]	349 subjects (621.8 person-years)[g]

[a] Cumulative search of the corporate safety database; 58 were received from spontaneous sources, 25 from Phase 1-3 clinical trials, 13 from Phase 4/solicited trials and 8 cases from the literature. Exposure in person time not calculated.

[b] Estimated using the median duration of exposure of 0.03 person-months/patient

[c] Estimated using the median duration of exposure of 60 person-months/patient

[d] Estimated using the median duration of exposure of 13.47 person-months/patient

[h] Study CA180056: Estimated using the median duration of exposure of 15.01 person-months/patient

[f] Estimated using the median duration of exposure of 60 person-months/patient

[g] Exposure calculated from Table 2.3-6 and Table 2.3-10

2.5 Post-Authorisation Experience

SPRYCEL® (dasatinib, BMS-354825) has been approved in several countries for the treatment of adults with newly diagnosed chronic myeloid leukaemia (CML) in chronic phase (CP), adults with chronic, accelerated, or myeloid or lymphoid blast phase CML with resistance or intolerance to prior therapy, including imatinib, adults with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukaemia (ALL) with resistance or intolerance to prior therapy and paediatric patients with Ph+ CML in chronic phase.

2.5.1 Post-authorisation Exposure

2.5.1.1 Method Used to Calculate Exposure

The estimated sales and average dose and duration of treatment, based on the prescribing information, are used to calculate the estimated number of patients treated. Keeping in mind that the dose and duration of therapy may depend on several factors (eg, age [adult, paediatric], body weight, renal function, specific treatment indication, therapeutic response), the methods and assumptions detailed below were used to arrive at an estimation of the number of patients treated with dasatinib.

The MAH reviewed all interval and cumulative exposure calculations from all PSURs/PBRERs that have been submitted to the EMA since marketing authorisation was granted in 2006. This review showed that assumptions regarding duration of treatment for individual patients were either not made or were not justified with real world data. Therefore, the MAH is providing a new calculation for interval and cumulative exposures which is explained in detail below. The MAH will continue to use these assumptions going forward and will modify the assumptions as appropriate based on the modifications in observed survival and treatment data detailed below.

The MAH reviewed the real-word interval global sales data in the context of estimation of patient exposure assumptions. Based on the current interval global sales data, the MAH has created a model to estimate the number of patients receiving dasatinib. The model and its assumptions are described below.

The methodology used to estimate the number of patients exposed to dasatinib utilised survival data as well as treatment data. First the observed survival of CML and ALL patients was obtained from the SEER*Stat program from National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER).[131] The most recent observed survival curves were similar between CML and ALL so the curve for CML was selected for the model. Detailed treatment data were obtained from SAEfetyWorks® version 5.1.0, a tool that provides access to administrative claims

and electronic health record databases in a common data model. SAEfetyWorks® data is based on U.S. claims; however, the MAH is not aware of a similar program that uses EU-based data.

By making the following assumptions regarding average dosage and duration of treatment, it is possible to estimate the number of patients treated with dasatinib during the current period:

- All patients were assumed to start on the 140 mg dose from Jun-2006 through Mar-2010. From April 2010 through the current period 98% of patients were assumed to start on the 100 mg dose and 2% of patients starting with the 140 mg dose.
- Based on data from administrative claims, 25% of 140 mg patients and 12% of 100 mg dosed patients changed to a lower dose of dasatinib each year.
- The mean length of treatment for the 140 mg, 100 mg and less than 100 mg dose groups in the real world data were 12 months, 24 months and 18 months, respectively.
- The average dose for the reduced dose was assumed to be 70 mg daily.

The calculation to build the model is demonstrated in the following example.

- In the period of 01-Jun-2006 to 31-Mar-2007 35,809,600 mg of dasatinib were sold. The number of patients receiving dasatinib in this period was 35,809,600 ÷ (140 X 275 [days in period]) = 1,118 patients.
- At the start of the next interval - 01-Apr-2007 to 30-Sep-2007 - the number of patients remaining alive and treated with 140 mg from the previous interval is calculated as 1,118 × 0.9035 (percentage still alive) × 0.75 (percentage still on treatment) = 758 patients.
- The number of patients that changed to a lower dose was calculated by taking the difference of the number of patients alive on 01-Apr-2007 and the number of patients alive and treated on 01-Apr-2007 and then multiplying this by 25%. The calculation is as follows: 1,118 × .9035 = 1010 (number of patients alive start of interval); then 1,010 - 758 = 252 (patients who discontinued or changed therapy) × 0.25 (percentage of patients who change therapy) = 63.
- In 01-Apr-2007 to 30-Sep-2007, 758 patients were receiving ongoing treatment at 140 mg, 63 patients received ongoing treatment at 70 mg and the remaining mg sold accounted for 1,162 patients at 140 mg. 758 × 140 × 182 (# of days in the interval) + 63 X 70 × 182 = 29,615,940 mg. 49,732,400 mg were sold in this period. 49,732,400 - 29,615,940 ÷ (140 × 182 [number of days in interval]) = 1,162 patients. The calculation then proceeds like this for each of the subsequent PSUR/PBRER intervals.

This estimate of the number of patients exposed should be interpreted with caution, taking into account the above-mentioned assumptions and the limitations of the available sales data.

2.5.1.2 Exposure

As described in Section 2.5.1.1, patient exposure can be estimated based on sales data received from IQVIA. These data, which represent an approximation of the total quantity of dasatinib sold, indicate that an estimated 9,036,652,100 mg were sold from 28-Jun-2006 through 31-Mar-2021.

Taking into account the available sales data and the assumptions provided as described above, the cumulative exposure of patients from 28-Jun-2006 through 31-Mar-2021 is estimated by adding the estimated number of new dasatinib users in each PSUR/PBRER period. Similarly, the

cumulative patient-years of exposure is estimated by adding the estimated number of patient-years exposure in each PSUR/PBRER period. The cumulative number of patients from 28-Jun-2006 through 31-Mar-2021 is estimated to be 110,406 and the cumulative number of patient-years of exposure is estimated to be 241,452.

Given the above-mentioned limitations and assumptions, this estimate of the cumulative number of patients treated from 28-Jun-2006 through 31-Mar-2021 should be interpreted with caution.

2.6 Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

Dasatinib is not a controlled substance and is administered with a prescription under medically controlled conditions. Given its class of action and lack of CNS effects, the potential for illegal use is low. Symptoms of dependence or withdrawal/rebound have not been formally investigated, but have not been reported in dasatinib clinical trials

2.7 Identified and Potential Risks

2.7.1 Identification of Safety Concerns in the Initial RMP Submission

Safety concerns identified in the initial submission of the RMP are summarized in Table 2.7.1-1.

Table 2.7.1-1: Safety Concerns in the Initial RMP

Important Identified Risks	Myelosuppression
	Fluid Retention
	Bleeding-related Events
	QT Interval Prolongation
Important Potential Risks	Severe Hepatotoxicities
	Photosensitivity
Missing Information	Reproductive and developmental toxicology
	Carcinogenicity
	Patients with Moderate to Severe Hepatic Impairment
Other Potential Concerns	Dasatinib interactions: dasatinib and potent CYP3A4 inhibitors or CYP3A4 substrates
	Drug interactions: dasatinib and other highly protein-bound medicinal products

2.7.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Dasatinib has a well-characterised safety profile that is reflected in the SmPC under Sections 4.4 and 4.8. New safety findings that are not categorized as either identified or potential risks in the list of safety concerns will be described, as applicable.

2.7.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Important identified risks	
Myelosuppression	Treatment with dasatinib causes low red blood cells (anemia), low white blood cells (needed to fight infection), and low platelets (needed for blood clotting). Patients with anemia can feel weak or tired. Patients with low white blood cells are at risk of a severe or life-threatening infection. Patients with low platelets are at risk of bleeding. The chance of a patient getting low blood counts depends upon whether they have Ph+ ALL or CML. If CML, the chance depends upon the phase of the disease (CP, AP, or BP). Patients with Ph+ ALL or advanced CML are more likely to get very low blood counts (as many as 8 out of 10 patients) than patients with CP CML (closer to 4 out of 10).
Fluid Retention	Dasatinib may cause various types of fluid retention. Fluid around the lining of the lung (pleural effusion) or heart (pericardial effusion), or fluid in the lungs (pulmonary oedema) may cause shortness of breath. Fluid in the abdomen (ascites) can cause abdominal discomfort or shortness of breath. Fluid under the skin (superficial oedema) can occur in various places in the body and may cause swelling or discomfort. Overall, severe fluid retention has been less common now that dasatinib is given once a day. In the study of once a day dasatinib in newly-diagnosed CML patients, fluid retention can occur anytime after starting treatment. After a minimum of 4 years of treatment, severe fluid retention was seen in 3% of patients (8/259) and approximately 1 out of 4 patients (62/259) had had a pleural effusion.
Bleeding Related Events	Bleeding has been very common in studies with dasatinib affecting more than 1 out of every 10 patients and can occur in any part of the body such as the brain, stomach or intestines. Severe and life-threatening or fatal bleeding has occurred. All types of bleeding were more common in the studies in CML and Ph+ ALL where dasatinib was given after imatinib or another therapy (22%) compared to when dasatinib was given as first line treatment with CML (5%).
QT Prolongation	Patients on dasatinib can rarely (1% chance or less) have changes in the electrical activity of the heart (QT prolongation). These changes could cause fainting or life-threatening irregular heart rhythms. Heart rhythm changes have been mild and have not caused any serious problems for the patients.
Important potential risks	
Severe Hepatotoxicities	Patients treated with dasatinib may be at increased risk of developing damage to the liver. Other drugs for CML treatment like dasatinib are known to cause liver damage. Patients on dasatinib have had damage to the liver develop. Patients with advanced phase CML or Ph+ ALL are more likely to show evidence of liver damage when on dasatinib. It is unknown if the damage was caused by the treatment or the leukaemia disease itself.

Table 2.7.1.2-1: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Risk Type	Risk-Benefit Impact
Photosensitivity	Photosensitivity is a recognized event associated with imatinib. Dasatinib treatment may result in phototoxicity in humans, however, based on non-clinical findings dasatinib treatment is not likely to be phototoxic in humans.
Missing Information	
Reproductive and developmental toxicology	Patients treated with dasatinib may be at risk of having a child with birth defects or a pregnancy with a damaged foetus. One seventy-eight pregnancies have been reported in female partners of male patients or female patients on dasatinib. The outcome is not known for all of the pregnancies. In male patients who have female partners who become pregnant, spontaneous abortions and premature delivery of a normal baby have been seen. However, most reported pregnancies end with normal deliveries. In female patients on dasatinib, dasatinib is almost always stopped once the woman knows she is pregnant. In 60 of the 104 cases, the diagnosis of pregnancy led to stopping or interruption of patient's dasatinib treatment. In 8 of these cases, women were either switched to (6) or resumed (2) ongoing therapy with interferon or alpha-interferon. Birth defects can occur in any pregnancy and spontaneous abortions occur in many pregnancies. It is possible that all the problems with pregnancy and infant and foetal abnormalities reported with dasatinib would have occurred even if the patients were not on dasatinib. However, it is also possible that dasatinib caused the abnormal pregnancies or spontaneous abortions in many or most cases.
Carcinogenicity	Patients in dasatinib studies could not have a recent second cancer so the effect of dasatinib on the growth of another cancer discovered either before, during, or after stopping dasatinib is not known.
Moderate to severe hepatic impairment	Safety data of patient population with co-morbidity of moderate to severe hepatic impairment (ie, AST or ALT above 2.5 times the upper normal limit of the normal range or bilirubin above 2 times the upper normal limit of the normal range) is not available.

2.7.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Table 2.7.2-1: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Safety Concern	
New	**Reasons for the addition:**
Thrombotic Microangiopathy added as an important identified risk	The MAH has added TMA as an important identified risk upon request from PRAC in the assessment report for the PSUR covering 28-Jun-2020 to 27-Jun-2021 (EMEA/H/C/PSUSA/00000935/202106).

Table 2.7.2-1: New Safety Concerns and Reclassification with a Submission of an Updated RMP

Safety Concern	
Previously classified important potential risk "Nephrotic Syndrome" reclassified as an important identified risk	The MAH has reclassified Nephrotic Syndrome from an important potential risk to an important identified risk upon request from PRAC in the assessment report for the PSUR covering 28-Jun-2020 to 27-Jun-2021 (EMEA/H/C/PSUSA/00000935/202106).

2.7.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

2.7.3.1 Presentation of Important Identified and Important Potential Risks

Table 2.7.3.1-1: Important Identified Risk: Myelosuppression

Important Identified Risk Myelosuppression	
Potential mechanisms	Unknown The majority of patients with CML or Ph+ ALL expressed some degree of haematologic toxicity. Myelosuppression is part of the natural history of most haematologic malignancies and is also a common side effect of most chemotherapeutic agents. Thus, the level of haematologic toxicity observed may partly be the result of the underlying leukaemic diagnosis and is in alignment with what can be expected in the heavily pre-treated patient population in each of the studies.
Evidence source and strength of evidence	Treatment with dasatinib is associated with anaemia, neutropaenia and thrombocytopaenia. Their occurrence is disease phase dependent and is more frequent in patients with advanced phase CML or Ph+ ALL than in CP CML. Myelosuppression is generally reversible and usually managed by withholding dasatinib temporarily and/or dose reduction.
Characterisation of risk	In CML patients with resistance or intolerance to prior imatinib therapy, cytopaenias (thrombocytopaenia, neutropaenia, and anaemia) were a consistent finding. The frequency of CTC Grade 3 or 4 neutropenia and thrombocytopaenia was higher in AP and myeloid BP (69-80% and 72-82%, for neutropaenia and thrombocytopenia, respectively) as compared with CP patients (47% neutropaenia and 41% thrombocytopaenia). Grade 3 or 4 anaemia was 55% and 75% in patients with AP CML and myeloid BP CML, respectively, as compared with 19% in patients with CP CML. In the Phase 3 dose-optimization study (CA180034) in CP CML, the frequency of neutropaenia, thrombocytopaenia and anaemia was lower in the dasatinib 100 mg QD than in the dasatinib 70 mg BID group. Cumulative grade 3 or 4 cytopaenias among patients treated with 100 mg QD were similar at 2 and 5 years including: neutropaenia (35% vs. 36%), thrombocytopaenia (23% vs. 24%) and anaemia (13% vs. 13%). In patients who experienced grade 3 or 4 myelosuppression, recovery generally occurred following brief dose interruption and/or reduction. Permanent discontinuation of treatment occurred in 5% of patients. Most patients continued treatment without further evidence of myelosuppression. In a multicenter, open-label Phase 3 study (CA180056) in 516 patients with newly diagnosed CP CML treated with either dasatinib or imatinib, after at

Table 2.7.3.1-1: Important Identified Risk: Myelosuppression

Important Identified Risk Myelosuppression	
	least 48 months since enrolment, the rates of Grade 3 to 4 neutropaenia (25.2% vs 20.9%), and anaemia (12.4% vs 9.3%) were comparable between the dasatinib and imatinib groups. The rate of Grade 3/4 thrombocytopaenia was higher in the dasatinib group compared with the imatinib group (19.8% vs 11.6%). [116] In a pooled paediatric population of 130 patients with CP-CML treated with dasatinib (CA180226), the rates of Grade 3 to 4 neutropaenia (20.2% vs 11.6%), anaemia (10.1% vs 4.7%), and thrombocytopaenia (7.8% vs 3.1%) were reported. 14.6% of patients developed severe (Grade 3-4) infections and one (1) patient reported Grade 3-4 drug related AE leading to discontunuation of study drug. In a pooled paediatric population of 58 patients with AP/BP-CML, Ph+ ALL or ALL treated with dasatinib (CA180018), the rates of Grade 3 to 4 neutropaenia (18.5% vs 57.4%), anaemia (29.6% vs 11.1%), and thrombocytopaenia (18.5% vs 59.3%) were reported. 17.2% of patients developed severe (Grade 3-4) infections and one (1) patient reported Grade 3-4 drug related AE leading to discontinuation of study drug. [132]. In a pooled paediatric population of 161 dasatinib in combination with chemotherapy treated paediatric patients (CA180372 and CA180204) with Ph+ ALL, the rates of Any Grade to Grade 3- 4 neutropaenia (16.1 vs 15.5%), anaemia (25.5% vs 24.8%), and thrombocytopaenia (13.0% vs 11.8%) were reported and 20.5% of patients developed severe (Grade 3-4) infections. Dasatinib-related AEs that led to treatment discontinuation occurred in 1 subject with a Grade 3 AE of thrombocytopenia. The patient took dasatinib tablet only. [130]
Risk factors and risk groups	The risk of myelosuppression is dose dependent. Myelosuppression is more frequent in patients with advanced phase CML or Ph+ ALL than in CP CML. Other risk factors: hepatic impairment (≥ Grade 2 alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin), CYP3A4 inhibitors, preexisting myelosuppression, prior imatinib treatment and chemotherapy, underlying haematologic malignancies.
Preventability	In patients with chronic phase CML, complete blood counts (CBCs) should be performed every two weeks for 12 weeks, then every 3 months thereafter, or as clinically indicated. In patients with advanced phase CML or Ph+ ALL, CBCs should be performed weekly for the first 2 months and then monthly thereafter, or as clinically indicated.
Impact on the risk-benefit balance of the product	Myelosuppression will impact the quality of life of an individual patient if: 1) treatment interruption, termination or dose reduction causes inadequate dasatinib dosing and disease-related symptoms, or 2) a severe or life-threatening infection or haemorrhage occurs. However, there are no quality of life data currently available from clinical trials evaluating effects of myelosuppression on individual patients.
Public health impact	None
MedDRA terms	Neutropenia, Thrombocytopenia, Anemia, Febrile neutropenia, Pancytopaenia, Bone marrow failure, Bone marrow toxicity, Aplastic anaemia and Agranulocytosis

Table 2.7.3.1-2: Important Identified Risk: Fluid Retention

Important Identified Risk Fluid Retention	
Potential mechanisms	Fluid retention with TKIs may be related to the inhibition of PDGFR inhibition.[43,133] Recent reports have also suggested dasatinib may induce a rapid mobilization and activation of cytotoxic, extravasation-competent lymphocytes.[134]
Evidence source and strength of evidence	Dasatinib may cause various types of fluid retention. Fluid around the lining of the lung (pleural effusion) or heart (pericardial effusion), or fluid in the lungs (pulmonary oedema) may cause shortness of breath. Fluid in the abdomen (ascites) can cause abdominal discomfort or shortness of breath. Fluid under the skin (superficial oedema) can occur in various places in the body and may cause swelling or discomfort.
Characterisation of risk	Dasatinib is associated with various types of fluid retention. In patients with resistance or intolerance to prior imatinib therapy receiving dasatinib, ARs such as pleural effusion, ascites, pulmonary oedema and pericardial effusion with or without superficial oedema were collectively described as "fluid retention". In patients with resistance or intolerance to prior imatinib therapy the use of dasatinib is associated with grade 3 or 4 fluid retention in 11% of patients. Superficial oedema: Any Grade 22%, Grade 3-4 1% Pleural effusion: Grade 3-4, 7% Of patients reporting a grade 3 or 4 pleural effusion, 87% reported improvement to grade 0-2. Ascites: Any Grade 1%, Grade 3-4, <1% Generalized oedema: Any Grade 4%, Grade 3-4 <1% Pericardial effusion: Grade 3-4 2% Pulmonary hypertension: Any Grade 1%, Grade 3-4 <1% Pulmonary oedema: Any Grade 2%, Grade 3-4 1% In a Phase 3 dose-optimization study (CA180034), fluid retention events (including pleural effusion and CHF/cardiac dysfunction) were reported less frequently with QD dosing (100 mg QD for CP CML than in patients treated 50 mg BID, 140 mg QD, and 70 mg BID. In a multicenter, open-label Phase 3 study (CA180056) in 516 patients with newly diagnosed CP CML treated with either dasatinib or imatinib, fluid retention was one of the most frequently reported ADRs reported in 19.4% and 34.5% of dasatinib-treated patients after a minimum of 12 or 48 months of therapy respectively.[116] In study CA180056, drug-related fluid retention was reported for fewer subjects in the dasatinib group (79 subjects, 34.5%) compared with the imatinib group (114subjects, 45%). The most common drug-related fluid retention AEs were pleural effusion (23.6%) and superficial oedema (13.2%) for dasatinib, and superficial oedema (37.2%) and generalized oedema (7.0%) for imatinib.[116] Pleural effusion, regardless of relationship to study drug, was reported for 62 subjects (24%) in the dasatinib group and 3 subjects (1.2%) in the imatinib group. Drug-related pericardial effusion was reported for 8 subjects (3.1%)

Table 2.7.3.1-2: Important Identified Risk: Fluid Retention

Important Identified Risk Fluid Retention	
	and 2 subject (<1%) in the dasatinib and imatinib groups, respectively. Drug-related pulmonary oedema was reported for 2 subjects (dasatinib group, Grade 1).[116] In a pooled paediatric population of 130 patients with CP-CML treated with dasatinib, drug related fluid retention was reported in 13 patients. The drug related fluid retention AEs reported were superficial oedema (6.9%), generalized oedema (1.5%) and CHF/Cardiac Dysfunction (2.3%). No Grade 3-4 drug related fluid retention was reported. In a pooled population of 58 patients with AP/BP-CML, ALL or ALL treated with dasatinib, drug related fluid retention was reported in 5 patients. The drug related fluid retention AEs reported were superficial oedema (3.2%) and plueral effusion (5.2%). Grade 3-4 drug related pleural effusion was reported in one (1) patient.[132] In a pooled paediatric population of 161 dasatinib in combination with chemotherapy treated paediatric patients (CA180372 and CA180204) with Ph+ ALL, the drug related fluid retention AEs reported were fluid retention (15 subjects, 9.3%), superficial oedema (8 subjects, 5.0%), pleural effusion (7 subjects, 4.3%), generalised oedema (3 subject, 1.9%), and ascites (3 subjects, 1.9%). The Grade 3-4 drug related fluid retention AEs reported were fluid retention (8 subjects, 5.0%), superficial oedema (3 subjects, 1.9%), pleural effusion (4 subjects, 2.5%), generalised oedema (1 subject, 0.6%), and ascites (2 subjects, 1.2%).[130]
Risk factors and risk groups	Risk factors include older age, fluid retention at baseline, prior imatinib treatment, and renal impairment. While the safety profile of dasatinib in the elderly population was generally similar to that in the younger population, the incidence of pleural effusion increases with age. For example, patients aged 65 years and older are more likely to experience fluid retention events and should be monitored closely.
Preventability	Most events are easily recognized and managed by health care providers and can be managed with dose reductions or dose interruption and supportive care. Patients who develop symptoms suggestive of pleural effusion such as dyspnoea or dry cough should be evaluated by chest X-ray.
Impact on the risk-benefit balance of the product	The impact on an individual patient depends upon the nature and severity of the fluid retention event. Whereas mild events such as grade 1 pleural effusion or superficial oedema may have little or no impact on quality of life, severe events may lead to symptoms such as shortness of breath and may rarely require procedures such as therapeutic thoracentesis. Data indicate that patients receiving dasatinib for initial treatment of CP CML who experience pleural effusion are no less likely than other patients to obtain cytogenetic and molecular response to dasatinib. However, there are no quality of life data currently available from clinical trials evaluating effects of fluid retention on individual patients.
Public health impact	None
MedDRA terms	Oedema, Generalized oedema, Pleural effusion, Pericardial effusion, Pulmonary oedema, Pulmonary hypertension, Ascites, Cardiac failure congestive, Fluid retention, Localized oedema, Oedema peripheral, Fluid overload, Hypervolaemia, Heart failure.

Table 2.7.3.1-3: Important Identified Risk: Bleeding Related-Events

Important Identified Risk Bleeding Related-Events	
Potential mechanisms	Most bleeding-related events were typically associated with severe thrombocytopaenia. Since the majority of patients with bleeding during dasatinib treatment have thrombocytopaenia, [135] this confounds the investigation of the additional effect of dasatinib on platelet function. Dasatinib has reversible effects on platelet activation in vitro and in vivo. Dasatinib weakly inhibits aggregation to a thrombin stimulus, but strongly inhibits platelet aggregation induced by collagen in a dasatinib dose-dependent manner.[136] In mouse platelets perfused over a matrix of collagen at a shear rate of $1500s^{-1}$ for 2 minutes (mimics physiological flow conditions), increasing doses of dasatinib also reduced thrombus volume in a dose-dependent manner (0, 12.5, 2.5, 5 mg/kg dasatinib). The 5 mg/kg dose in mice is similar to the 100 mg QD dose used in humans. In a separate *in vivo* mouse bleeding time assay, mice were given dasatinib and bleeding was induced by tail tip amputation. Four hours after dasatinib, bleeding time increased in a dose dependant manner (0, 1.25, 2.5, and 5 mg/kg doses used). Twenty-four hours later, the effects of dasatinib on bleeding time was weak and was no longer detectable by 48 hours. Thrombus formation under physiological flow conditions was measured in a single female CP CML patient with a complete haematological response taking 100 mg QD of dasatinib. After 24 hours, thrombi formed on collagen fibers were much bigger in surface and volume than at 24 hours demonstrating rapid reversibility of dasatinib's effect on platelet activation. This is consistent with the PK of dasatinib with a short 3-5 hour half-life. The reversibility noted in assays of both platelet aggregation and thrombus formation clearly indicates that dasatinib behaves differently than the irreversible platelet inhibitor, aspirin. The effects of dasatinib on platelet activation may also contribute to bleeding in addition to the thrombocytopaenia.
Evidence source and strength of evidence	Bleeding has been very common in studies with dasatinib affecting more than 1 out of every 10 patients and can occur in any part of the body such as the brain, stomach or intestines. Severe and life-threatening or fatal bleeding has occurred.
Characterisation of risk	Haemorrhage is reported at a frequency of "very common" (1/10) in dasatinib clinical trial and post marketing reports. Of the 2182 dasatinib treated subjects resistant or intolerant to imatinib, drug-related haemorrhage occurred in 22% (all grades) patients with 6% as severe (Grade 3-4). Of these: GI bleeding: All Grades 8.7%, Grade 3-4 4.5% CNS bleeding: All Grades <1%, Grade 3-4 <1% In patients with CP CML (CA180034), drug-related GI bleeding events were reported in 2% and 4% of patients in the 100 mg QD and 70 mg BID groups, respectively. In patients with advanced phase CML (CA180035), drug-related GI bleeding events were reported in 8% and 12% of patients in the 140 mg QD and 70 mg BID groups, respectively In a multicenter, open-label Phase 3 study (CA180056) in 516 patients with newly diagnosed CP CML treated with either dasatinib or imatinib, drug-related bleeding was infrequent and comparable between the dasatinib and imatinib groups (13 subjects, 5.0% vs 12 subjects, 4.7%). Of these subjects,

Table 2.7.3.1-3: Important Identified Risk: Bleeding Related-Events

Important Identified Risk Bleeding Related-Events	
	1 dasatinib-treated subject and 2 imatinib-treated subjects reported severe (Grade 3 to 4) drug-related bleeding. Among all bleeding events, drug-related GI bleeding was reported for 2 (0.8%) subjects in the dasatinib group and none in the imatinib groups,, and was severe in both subjects (Grade 3) but did not lead to discontinuation. CNS bleeding was reported for 1 dasatinib-treated subject (Grade 4) but did not lead to discontinuation.[116] In a pooled paediatric population of 130 patients with CP-CML treated with dasatinib, there were no cases of drug-related severe CNS haemorrhage reported. In a pooled population of 58 patients with AP/BP-CML, ALL or ALL treated with dasatinib, there were no cases of drug-related severe CNS haemorrhage reported.[132] In a pooled paediatric population of 161 dasatinib in combination with chemotherapy treated paediatric patients (CA180372 and CA180204) with Ph+ ALL, Grade 3-4 drug-related bleeding related events (haemorrhage) was reported in 9 patients. There were no cases of drug-related severe CNS haemorrhage reported.[130]
Risk factors and risk groups	Patients with leukaemia, severe thrombocytopaenia, coagulation disorder, cardiovascular disorders, and patients who take medicinal products that inhibit platelet function or anticoagulants. Most bleeding related events in these patients were typically associated with grade 3 or 4 thrombocytopaenia CNS haemorrhage is a known complication of leukaemia and, like GI haemorrhage, typically results from severe thrombocytopaenia or platelet dysfunction. GI haemorrhage is a known comorbid condition in an acutely ill population of Leukaemic patients, typically resulting from thrombocytopaenia or platelet dysfunction. Among these subjects without significant thrombocytopaenia, the frequency of haemorrhage events was similar between the dasatinib and imatinib groups (any grade: 9.4% vs 9.1%; Grade 3 to 4: 1.8% vs 1.5%). There was a trend toward more frequent "other" (defined as ear haemorrhage, epistaxis, gingival bleeding, haematoma, haematuria, haemoptysis, petechiae, and scleral haemorrhage) haemorrhage events with imatinib (dasatinib: 6.4%, imatinib: 8.1%). These data suggest that among subjects with adequate platelet counts for normal hemostasis, bleeding events were infrequent and low grade among both treatment groups.
Preventability	Caution should be exercised if patients are required to take medicinal products that inhibit platelet function or anticoagulants. Most events are easily recognized with periodic CBC monitoring and managed by health care providers and can be managed with dose reductions or dose interruption and supportive care.
Impact on the risk-benefit balance of the product	The impact of an individual patient depends on the nature and severity of the bleeding events. Minor bleeding events are not expected to have a significant effect on quality of life. In contrast, severe events can be associated with serious morbidity and mortality. The specific consequences will depend upon the volume of bleeding and specific site. However, there

Table 2.7.3.1-3: Important Identified Risk: Bleeding Related-Events

Important Identified Risk Bleeding Related-Events	
	are no quality of life data currently available from clinical trials evaluating effects of bleeding-related events on individual patients.
Public health impact	None
MedDRA terms	Haemorrhages and Necrotising enterocolitis (NEC), Nervous system haemorrhagic disorders and Gastrointestinal Haemorrhages. **Haemorrhages-related terms:** Conjunctival haemorrhage, Petechiae, Epistaxis, Haematoma, Respiratory tract haemorrhage, Haemoptysis, Ecchymosis, Purpura, Haematuria, Menorrhagia and Polymenorrhagia. **GI bleeding-related terms:** Gingival bleeding, Rectal haemorrhage, Lower gastrointestinal haemorrhage, Upper gastrointestinal haemorrhage, Gastric haemorrhage, and Melaena. **CNS bleeding-related terms:** Haemorrhage intracranial, Cerebral haemorrhage, Subdural haematoma, and Extradural haematoma.

Table 2.7.3.1-4: Important Identified Risk: QT Prolongation

Important Identified Risk QT Prolongation	
Potential mechanisms	Dasatinib activity in vitro in hERG and Purkinje fiber assays suggested a potential for prolongation of cardiac ventricular repolarisation (QT).
Evidence source and strength of evidence	Dasatinib may increase the risk of prolongation of QTc in patients including those with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking antiarrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy.
Characterisation of risk	In Phase 2 clinical trials in patients with leukaemia treated with dasatinib (n=865), the mean changes from baseline in QTcF were 4 - 6 msec; the upper 95% confidence intervals (CIs) for all mean changes from baseline were < 7 msec. Of the 2,182 patients who received dasatinib in Phase 2/3 studies in the second line, 14 (0.9%)[92] patients had QTc prolongation reported as an ADR. Twenty-one patients (1%) experienced a QTcF > 500 msec. In a multicenter, open-label Phase 3 study (CA180056) in 516 patients with newly diagnosed CP CML treated with either dasatinib or imatinib, ECGs were performed at baseline and after 4 weeks of study treatment. QTc (F) intervals and changes from baseline were similar among treatment groups. Two subjects had a QTc (F) > 500 msec, 1 in each treatment group (0.4%). The median QTc (F) change from baseline was lower with dasatinib compared with imatinib (3.0 msec vs 8.2 msec). These data are consistent with that reported in subjects with treatment-refractory leukaemia treated with dasatinib in Phase 2 clinical studies, where the mean changes from baseline in QTc interval using QTc (F) were 4 to 6 msec, the upper 95% CIs for all mean changes from baseline were < 7 msec, and 21 subjects (1%) experienced a QTc (F) > 500 msec.[116] With a minimum of 48 months of follow-up, no new AEs of QT prolongation were reported in the dasatinib group.[114,137]

Table 2.7.3.1-4: Important Identified Risk: QT Prolongation

Important Identified Risk QT Prolongation	
	In a pooled paediatric population of 130 patients with CP-CML treated with dasatinib, AEs of QT prolongation were reported in 2 patients.[132] In a pooled paediatric population of 161 dasatinib in combination with chemotherapy treated paediatric patients (CA180372 and CA180204) with Ph+ ALL, drug-related AEs of QT prolongation were reported in 3 patients.[130]
Risk factors and risk groups	Patients with hypokalaemia or hypomagnesaemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicinal products or other medicinal products which lead to QT prolongation, and cumulative high dose anthracycline therapy. Other risk factors include baseline QT prolongation, cardiac history (eg, CHF, bradycardia, MI), elderly, and female.[137]
Preventability	Dasatinib should be administered with caution to patients who have or may develop prolongation of QT. These include patients with Hypocalcaemia, hypokalaemia, or hypomagnesaemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicinal products or other medicinal products which may lead to QT prolongation, and cumulative high dose anthracycline therapy. Hypocalcaemia, hypokalaemia, or hypomagnesaemia should be corrected prior to dasatinib administration.
Impact on the risk-benefit balance of the product	There is minimal impact from QT prolongation unless a severe or life-threatening arrhythmia develops. Severe or life-threatening arrhythmias could be associated with significant morbidity (hospitalisation, medical procedures, etc) and mortality. However, there are no quality of life data currently available from clinical trials evaluating effects of QT prolongation on individual patients
Public health impact	None
MedDRA terms	Electrocardiogram QT prolonged, Electrocardiogram QT interval abnormal.

Table 2.7.3.1-5: Important Identified Risk: Pulmonary Arterial Hypertension (PAH)

Important Identified Risk Pulmonary Arterial Hypertension (PAH)	
Potential mechanisms	Unknown
Evidence source and strength of evidence	Dasatinib may increase the risk of developing pulmonary arterial hypertension (PAH) which may occur any time after initiation, including after more than 1 year of treatment. Manifestations include dyspnea, fatigue, hypoxia, and fluid retention. PAH may be reversible on discontinuation of dasatinib.
Characterisation of risk	The true frequency and incidence rates for PAH are unknown. A comprehensive,[138] cumulative search of the Corporate safety database was performed on cases reporting AEs/SAEs (MedDRA version 16) encoding to

Table 2.7.3.1-5: Important Identified Risk: Pulmonary Arterial Hypertension (PAH)

Important Identified Risk Pulmonary Arterial Hypertension (PAH)	
	the HLT "Pulmonary Hypertensions" covering the date range of 28-Jun-2006 (international birth date) to 27-Jun-2013. The search identified 86 cases of PAH, of which 39 were confirmed to have PAH on the basis of RHC. Of these 39 cases, capillary wedge pressure values were provided in 21 cases and in the remainder PAH was reported. To supplement the previous cumulative search through 27-Jun-2013, the Company performed an interval search (28-Jun-2013 to 27-Jun-2014) of the Corporate safety database on cases reporting the PT of "Pulmonary Arterial Hypertension". The interval search identified 35 additional cases of reported PAH, of which 11 were confirmed to have PAH on the basis of right heart catheterization (RHC). The remainder of the cases were reported to have PAH at the time of RHC. Of these 11 cases, capillary wedge pressure values were provided in 6, of which all were < 15 mm. Mean Pulmonary artery pressure (mPAP) was reported in 8 of these cases, of which all were >25 mm. Of the 35 cases, 11 were spontaneously reported from worldwide sources, 6 were derived from the published scientific literature, and 18 were received from post-marketing trials. All cases were assessed as serious. A supplemental search of the Corporate safety database from 28-Jun-2014 to 27-Jun-2017 retrieved 76 cases with an adverse event coded to the PT Pulmonary arterial hypertension (MedDRA version 20.0); all cases were assessed as serious (33 spontaneous, 27 literature post-marketing, 10 solicited, 5 clinical trial and 1 literature clinical trial). These 76 cases describe 39 males and 33 females (gender not reported in 4) ranging in age from 23 years to 71 years (mean=53 years; n=71). Time to onset of the PAH (from the first dose) event ranged from 40 days to 2822 days (mean=1228 days; n=40). The outcome of the PAH event included recovered/resolved in 19, not recovered/not resolved in 17, recovering/resolving in 13 and unknown in 25. There were 2 fatal outcomes for the PT PAH: [redacted] (accompanied by pleural effusion, pericardial effusion and cardiac failure) and [redacted] (preceded by myocardial infarction in a patient taking concomitant unspecified diet pills, with a history of beta thalassemia, hypertension and diabetes mellitus). Clinical Database: In the pooled population of CML and Ph+ ALL patients treated with dasatinib monotherapy in clinical trials, there were 6 subjects with reported PAH. No cases reported a RHC. Only 2 cases were reported as AE's and would not be represented in the corporate safety database search. In a pooled paediatric population of 130 patients with CP-CML treated with dasatinib, there were no cases of drug-related PAH reported. In a pooled population of 58 patients with AP/BP-CML, ALL or ALL treated with dasatinib, there were no cases of drug-related PAH reported.[132] In a pooled paediatric population of 161 dasatinib in combination with chemotherapy treated paediatric patients (CA180372 and CA180204) with Ph+ ALL, there were no cases of drug-related PAH reported.[130]
Risk factors and risk groups	The cumulative search through 27-Jun-2013, provided the following information on each risk group/risk factor:

Table 2.7.3.1-5: Important Identified Risk: Pulmonary Arterial Hypertension (PAH)

Important Identified Risk Pulmonary Arterial Hypertension (PAH)	
	Gender and age: As with all post-marketing the reporting age and gender of patients was not reported in all cases. Gender was provided in 75 of the reported 86 cases of PAH (35 males, and 40 females). Age and gender was provided in all 39 cases of catheter confirmed PAH. In the catheter confirmed PAH group, 25 of the 39 reported cases were female. The median age of patients was slightly lower in the catheter confirmed PAH group when compared to the total group. Of note, the median age of subjects enrolled in the clinical trial program in second line therapy is 56 years. The median age of patients with catheter confirmed PAH was 53 years. **Underlying disease:** The majority of patients receiving dasatinib were being treated for CML or ALL per the licensed indications, although occasional cases of solid tumors were reported with PH from other clinical trials with dasatinib. A single literature report of PAH associated with dasatinib use in metastatic malignant melanoma is the only report of off label use and PAH. **Prior medical history:** Of the 39 subjects with catheter confirmed PAH, 5 had prior medical histories of fluid retention events (pleural effusion, generalized oedema) reported with dasatinib or prior TKI treatment before the episode of PAH. An additional 10 had significant medical history of relevant serious cardiovascular-pulmonary disease including miliary tuberculosis (TB) (2), coronary artery disease requiring coronary stenting (2), myocardial infarct (1), angina (1), hypertension (1), heavy smoking (1), femoral thrombosis (1) and chronic obstructive pulmonary disease (1). **Time to onset:** Of the 86 cases of reported PAH (catheter confirmed and otherwise), the time to onset was reported in 58 cases. The time to onset of reported PAH after the initiation of treatment with dasatinib in these 58 cases ranged from 0.06 months to 84 months (mean = 30 months). The time to onset after the initiation of treatment with dasatinib in the PAH cases confirmed by RHC ranged from 0.26 months to 75 months (mean = 29 months). The interval search (28-Jun-2013 to 27-Jun-2014) provided the following information on each risk group/risk factors: **Gender and age:** Gender was reported in 25 of the 35 cases of PAH (11 males and 14 females). Age was reported in 25 cases. In these cases, the mean age was 55.6 years (range 16-73 years). **Underlying disease:** Of the 35 cases with reported PAH, all but 2 were reported as being treated for CML or ALL per the licensed indications. In one case, the indication was not reported, and a single spontaneous report of PAH associated with dasatinib use in metastatic malignant melanoma was the only report of off label use in these cases. **Prior medical history:** Of the 35 patients with PAH, several cases had relevant pre-existing or co-morbid cardiopulmonary or connective tissue disease, including preexisting arterial hypertension (9), pre-existing cardiac valvular disease (2), atrial fibrillation (2), including 1 with cardiomegaly, scleroderma (1), chronic obstructive pulmonary disease (1), pneumonia legionella (1), smoking history (3), sleep apnea (2), and pulmonary tuberculosis (1).

Table 2.7.3.1-5: Important Identified Risk: Pulmonary Arterial Hypertension (PAH)

Important Identified Risk Pulmonary Arterial Hypertension (PAH)	
	Time to onset: Time to onset of PAH after initiation with dasatinib treatment was reported in 20 of the 35 cases. The time to onset in these cases ranged from 0.33- 66 months (mean = 29.5 months).
Preventability	No adequate data are available on potential preventive or mitigating measures for PAH. Early consideration of the diagnosis of PAH may be helpful in mitigating the severity through early detection. An electronic case report form (e-CRF) has been developed and is implemented in all ongoing and planned dasatinib studies in order to characterize PAH cases. A questionnaire is also used to obtain additional information about diagnosis and treatment of PAH in spontaneous and post-marketing reports. In the cumulative search through 27-Jun-2013, action with dasatinib was provided in 57/86 (66%) of PAH cases reported. At the time of last follow up dasatinib had been discontinued in 56 (65%) of patients, interrupted in 4 (7%) and dose reduced in 1 (2%). Current guidance in the dasatinib SmPC dated 21-Nov-2013 is that dasatinib should be discontinued if PAH is diagnosed. In many subjects, an important part of treatment was the treatment of concurrent cardio-pulmonary illness most often diuretics and steroids for pleural effusion (rarely with additional thoracocentesis), antibiotics for chest infections, improved treatment for asthma etc. Specific treatment for PAH included endothelin (ET) receptor antagonists (bosentan) and/or phosphodiesterase type 5 inhibitors (sildenafil and tadalafil) in twelve (12) subjects and each of these agents: adenosine, diltiazem, dobutamine, noradrenalin and sodium nitroprusside in individual subjects. In the interval search (28-June 2013 to 27-June 2014), action with dasatinib was provided in 16 of the 35 PAH cases reported. At the time of last follow up, dasatinib had been discontinued in all of these 16 patients. In the remaining 19 cases, no action was recorded. Treatment was reported for 13 of the 35 PAH cases. More than 1 treatment medication was reported for many of the patients. Treatment included the phosphodiesterase type 5 inhibitors-sildenafil or tadalafil (5); ET receptor antagonist bosentan (2); Beta-blocker with nitric oxide vasodilatory effect, nebivolol (1); diuretics (7); nitric oxide (2 cases); and prostacyclin analog, Iloprost (2). In the 9 cases with reported pleural effusion, reported treatment included diuretics (4), and phosphodiesterase type 5 inhibitors, sildenafil (2),). Treatment with Iloprost was reported in 1 patient with a pleural effusion, and treatment was not reported in 1 patient. Use of steroids was reported in 1 patient in conjunction with diuretics. Clinical database: In the pooled clinical trial population, of the 2 AE cases with reported PAH, a 77-year-old male was reported to have PAH concurrently with SBE, pleural effusion, and mitral and tricuspid regurgitation, no action was reported for the PAH (grade 2), and no treatment was reported; however, it was reported that the drug was interrupted temporarily for the underlying pleural effusion (grade 2) and later restarted. The SBE was reported as a SAE, but PAH was reported as an AE. The other AE case of a 47-year-old male [redacted] who developed grade 2 PAH two and half months after initiation of dasatinib therapy reported that drug was interrupted and treatment was required. The only treatments reported were mucolytic agents.

Table 2.7.3.1-5: Important Identified Risk: Pulmonary Arterial Hypertension (PAH)

Important Identified Risk Pulmonary Arterial Hypertension (PAH)	
Impact on the risk-benefit balance of the product	PAH is a rare event with dasatinib. Common concurrent findings in patients with PAH were fluid retention and symptoms of dyspnoea on exertion, and fatigue. However, there are no quality of life data currently available from clinical trials or other sources evaluating effects of PAH on individual patients. Data from the Company searches revealed that, in cases confirmed for PAH, the event improved or resolved when treatment with dasatinib was stopped.
Public health impact	None
MedDRA terms	"pulmonary hypertensions" is comprised of the following PTs: cor pulmonale, cor pulmonale acute, cor pulmonale chronic, Eisenmenger's syndrome, portopulmonary hypertension, PAH, PA wall hypertrophy, pulmonary hypertension and pulmonary hypertensive crisis

Table 2.7.3.1-6: Important Identified Risk: Pregnancy-Related Malformative or Foeto/neonatal Toxicity

Important Identified Risk Pregnancy-Related Malformative or Foeto/neonatal Toxicity	
Potential mechanisms	Nonclinical reproductive toxicity studies indicate that dasatinib is an embryo-foetal toxicant in pregnant female rats and rabbits but not a reproductive toxicant in male rats at clinically efficacious doses. However the mechanism is unknown.
Evidence source and strength of evidence	Based on limited human data, dasatinib can cause foetal harm when administered to a pregnant woman. Adverse pharmacologic effects of dasatinib including hydrops fetalis, foetal leukopenia, and foetal thrombocytopenia have been reported with maternal exposure to dasatinib Advise females of reproductive potential to avoid pregnancy, which may include the use of effective contraception, during treatment with dasatinib and for 30 days after the final dose
Characterisation of risk	A cumulative search of the corporate safety database through 27-Jun-2014 identified a total of 189 (173 HPC, 16 non-HPC) cases involving dasatinib exposure during pregnancy. Of these 189 cases, 111 were received from spontaneous sources, 53 from clinical trials, 17 from phase 4/solicited studies, and remaining eight cases were received from the literature. Eighty-two of the 189 cases involved paternal exposure and remaining 107 cases involved maternal exposure. • **Female Partners of Male Patients**: • A total of 82 cases through 27-Jun-2014 reported pregnancies in female partners of males treated with dasatinib. Of the 82 cases, 50 were received from spontaneous sources, 28 from phase 1-3 clinical trials, and remaining 4 from phase 4/solicited clinical trials. Age was reported in 45 cases and ranged from 24 years to 49 years (mean age = 34 years and 7 months). • **Female Patients**:

Table 2.7.3.1-6: Important Identified Risk: Pregnancy-Related Malformative or Foeto/neonatal Toxicity

Important Identified Risk Pregnancy-Related Malformative or Foeto/neonatal Toxicity	
	A total of 107 cases through 27-Jun-2014 were identified involving female patients who were exposed to dasatinib during pregnancy. Please note that 1 subject had 3 separate cases reporting pregnancies of which only 1 pregnancy had occurred while on active treatment with dasatinib. Further, 2 cases were identified as duplicate cases. Therefore, 104 on-treatment pregnancies with dasatinib were reviewed. Of the 104 cases, 58 were received from spontaneous sources, 25 from phase 1-3 clinical trials, 13 from phase 4/solicited trials and remaining 8 cases were received from the literature. Age was reported in 84 cases and ranged from 17-years to 44-years (mean age = 29-years and 7-months). A supplemental search of the corporate safety database was performed from 28-Jun-2014 to 27-Jun-2017. The following initial significant foeto/neonatal events were identified (MedDRA 20.0): **Maternal exposure:** Congenital hypothyroidism [redacted]: The 28-year-old mother ([redacted]) received dasatinib for CML for the first 3 weeks of her pregnancy (no contraception used) and her 13 day old infant was diagnosed with congenital hypothyroidism. **Paternal exposure:** Syndactyly: A baby of unknown gender had congenital syndactyly while the baby's father was exposed to dasatinib. Scoliosis The father received dasatinib for CML and levothyroxine sodium (an additional suspect medication) before and during his partner's pregnancy. The female child had significant thoracic-lumbar scoliosis evaluated at 40 degrees and delayed learning to walk at 17 months. She had axial hypotonia and significant gibbosity evaluated at 4 cm in right thorax lumbar region as well as a blind sinus above the gluteal fold (no malformation of cranial-rachidial hinge and no vertebral malformations).
Risk factors and risk groups	**Female Partners of Male Patients**: Seven [redacted] of the 82 cases confirmed that the female partner and/or male patient, did not use any form of contraception at the time of conception. Additionally, only 4 cases [redacted] provided details on contraception use, described as double barrier contraception and condoms (2 cases each). **Female Patients**: Five [redacted] and [redacted] of the 104 cases confirmed that the female partner and/or male patient, did not use any form of contraception at the time of conception. Additionally, 23 cases provided details on contraception use as the following: oral contraception (9), abstinence, condoms (3 each), barrier method, unspecified contraception (2 each), and abstinence/condom, contraception via temperature measurement, intramuscular contraceptive, and "safe periods" (1 each).
Preventability	Dasatinib should not be used during pregnancy. Both sexually active men and women should use effective methods of contraception during treatment to prevent pregnancy.
Impact on the risk-benefit balance of the product	**Female Partners of Male Patients**: The pregnancy outcomes was provided in 32 of the 82 cases involving paternal exposure as the following: normal newborn (25 cases), abortion spontaneous (4), live birth (1), infant (1), and abortion induced (1); the pregnancy outcome was unknown or unspecified in the remaining 50 cases. In case reporting pregnancy outcome of infant, a 42-

Table 2.7.3.1-6: Important Identified Risk: Pregnancy-Related Malformative or Foeto/neonatal Toxicity

Important Identified Risk Pregnancy-Related Malformative or Foeto/neonatal Toxicity	
	year-old female partner became pregnant while he was receiving dasatinib 140 mg QD for CML. The obstetrical complications or maternal medical condition during pregnancy were unknown. The mother delivered a newborn female for which foetal/neonatal outcome was unknown. At the time of the report, study therapy remained ongoing. In a case reporting pregnancy outcome of live birth, a 35-year-old female partner delivered a male baby (via Cesarean section) who was born with bilateral syndactyly of feet and ear cartilage was not fully formed. There was no therapeutic impact on male patients as all continued treatment as planned. **Female Patients**: The overall impact on the women was significant with many stopping or interrupting treatment for underlying disease for the duration of pregnancy or undergoing elective or therapeutic abortion. Of the total 104 cases, the action taken with the dasatinib therapy was reported in 69 cases. In these 69 cases, the diagnosis of pregnancy either led to stopping (40) or interruption (20) of patient's dasatinib treatment. In 9 other cases, no action was taken with dasatinib therapy. The action taken with dasatinib therapy was unknown or unspecified in the remaining 35 cases. In 8 of these cases, women were either switched to (6) or resumed (2) ongoing co-suspect therapy with an interferon. Fifty-seven of the 104 cases reported the following pregnancy outcomes: normal newborn (20 cases), abortion induced (19), abortion spontaneous (8), live birth (5), premature delivery (2), abortion, and small for dates baby (1 case each). In cases reporting pregnancy outcome of live birth, 2 cases reported normal live births, in 1 case the foetal/neonatal outcome was unknown, and 2 other cases involved foetal/neonatal abnormalities of pyelocaliectasis and hydrops foetalis, pulmonary hypoplasia, pleural effusion, and foetal growth restriction. Pregnancy outcome was unknown or unspecified in the remaining 47 cases.
Public health impact	Due to the potential for infant and foetal anomalies, dasatinib should not be used during pregnancy.
MedDRA terms	Congenital, familial, and genetic disorders, Abortions and still birth, Foetal complications, Neonatal and perinatal conditions

Table 2.7.3.1-7: Important Identified Risk: Nephrotic Syndrome

Important Identified Risk Nephrotic Syndrome	
Potential mechanisms	The precise mechanism for this potential risk is unknown. No clinical studies were conducted with dasatinib in subjects with decreased renal function. Clinical studies in subjects with newly diagnosed CP CML excluded subjects with serum creatinine concentration > 3 times the upper limit of the normal (ULN) range, and studies in subjects with CP CML resistant to or intolerant of prior imatinib therapy excluded subjects with serum creatinine concentration > 1.5 times the ULN range. Since the renal clearance of dasatinib and its metabolites is < 4%, a decrease in total body clearance is not expected in subjects with renal insufficiency.

Table 2.7.3.1-7: Important Identified Risk: Nephrotic Syndrome

Important Identified Risk Nephrotic Syndrome	
Evidence source and strength of evidence	Nephrotic syndrome is a constellation of clinical and laboratory features of renal disease. Symptoms and signs include heavy proteinuria (protein excretion greater than 3.5 g/24hours), hypoalbuminemia (less than 3 g/dL), and peripheral oedema. Although untreated or unrecognized Nephrotic Syndrome may be a serious condition, the symptoms, signs and laboratory abnormalities (peripheral oedema, proteinuria and hypoalbuminuria) are easily recognized by trained medical providers.
Characterisation of risk	A cumulative search of the corporate safety database through 21-Sep-2016 was performed to identify all spontaneous, literature and clinical trial cases (all causality) in which dasatinib was considered a suspect or interacting drug and at least one of the reported adverse event terms in the case was mapped to the Preferred Term (PT) of Nephrotic syndrome using MedDRA Version 19.0. The incidence of nephrotic syndrome is unknown but it is thought to be uncommon. Thirty two (32) cases were identified and of the 32 cases, 20 were spontaneously reported from worldwide sources, 4 were derived from the published scientific literature, 5 were received from clinical trials and 3 were solicited cases. All 32 cases qualified for classification as serious. These 32 cases described 17 females and 11 males (gender not provided in 4 cases) ranging in age from 3 years to 78 years (mean = 43; n=27). Indication for dasatinib was reported as chronic myeloid leukaemia (CML) in 21 cases, acute lymphocytic leukaemia (ALL) in 4 cases, prostate cancer in 2 cases (CA180-227 study) and glioma in 1 case (indication for dasatinib use unknown or not reported in 4 cases). The action taken with dasatinib was withdrawn in 15, interrupted in 7, dose decreased in 1 and no changes in 2 (action taken was unknown/not reported in 7 cases). 16 of the 32 cases of nephrotic syndrome were either related or a relationship could not be excluded based on resolution or improvement of nephrotic syndrome when dasatinib was withdrawn or dose reduced or when another tyrosine kinase inhibitor was substituted for dasatinib. The other 16 cases did not contain enough information or were confounded by other factors which made it difficult to make a reasonable medical assessment.
Risk factors and risk groups	At the time of this report there were no known risk groups or factors related to this potential risk specifically associated with dasatinib treatment.
Preventability	No clear prevention exists. However, once recognized, dasatinib should be interrupted or discontinued if appropriate. Following review of the Corporate safety database and available literature, nephrotic syndrome associated with dasatinib has been found to respond to dose reduction or discontinuation or switching to an alternative BCR-ABL tyrosine kinase inhibitor.
Impact on the risk-benefit balance of the product	Nephrotic syndrome is a constellation of clinical and laboratory features of renal disease. Symptoms include heavy proteinuria (protein excretion greater than 3.5 g/24 hours), hypoalbuminemia (less than 3 g/ dL), and peripheral oedema. Various medical conditions and medications have been associated with nephrotic syndrome.
Public health impact	None.
MedDRA terms	Nephrotic syndrome

Table 2.7.3.1-8: Important Identified Risk: Thrombotic Microangiopathy

Important Identified Risk Thrombotic Microangiopathy	
Potential mechanisms	TMA syndromes are extraordinarily diverse and there are likely multiple mechanisms for toxic drug-mediated TMA including endothelial dysfunction, increased platelet aggregation, and diminished VEGF function in renal endothelial cells.[139] Martino described a 24-year-old female with imatinib resistant CML who presented with dasatinib-induced thrombocytopenic purpura (TTP)/HUS that resulted in terminal renal failure and renal transplantation several years after the initial episode of TMA and renal failure.[140] Although ADAMSTS13 level was reduced, it was still in the normal range and no anti-ADAMSTS13 antibodies were present. The authors postulated direct endothelial toxicity resulting in lysis of endothelial cells and platelet aggregation. Both bevacizumab and sunitinib inhibit VEGF function through binding of the molecule or its receptor and both have been associated with TMA in renal cell and other tumors perhaps through down regulation of pro-angiogenic proteins including VEGF and its receptors.[141] This mechanism does not seem likely for dasatinib, as it is a weak inhibitor of VEGF Receptor and appears to be rarely associated with TMA.
Evidence source and strength of evidence	George, JN, Nester, CM[139] Martino et al[140] Mittal et al[141] Corporate Safety Database.
Characterisation of risk	**Frequency** A review of marketing authorizations holders' clinical trial database (2712 patients with CML exposed to dasatinib, the review included 5 and 7 years follow up, where available, 188 pediatric patients and 161 patients with ALL) did not identify any case of TMA. At the time of the review for TMA, it was estimated that approximately 64,000 patients were exposed to dasatinib during the availability of dasatinib for the prescription. Overall, based on the corporate safety database and literature review, TMA was reported in 2-7 patients exposed to dasatinib in whom an association between the reported event and dasatinib administration could not be excluded. A supplemental search of the corporate safety database for the interval from 28-Jun-2019 to 27-Jun-2020 with the PTs coded, Disseminated intravascular coagulation, Haemolysis, Haemolytic uraemic syndrome, Microangiopathic hemolytic anemia, Scleroderma, Thrombotic microangiopathy (TMA), Thrombotic thrombocytopenic purpura, Microangiopathy, Autoimmune hemolytic anemia, Atypical hemolytic uraemic syndrome (MedDRA version 23.0), identified a total of five cases. All cases reported were HCP confirmed, two were from literature post-marketing and the three were spontaneous. Three of the reported 5 patients were female and in 2 gender was not reported. One of the 5 patients the outcome was reported as recovering/resolving and in four the outcome was unknown. Two of the 5 cases are described in the same article (Koshinda T et. al.). Of which the first case ([redacted]) reported a 48-year-old female with

Table 2.7.3.1-8: Important Identified Risk: Thrombotic Microangiopathy

Important Identified Risk Thrombotic Microangiopathy	
	CML, who developed signs and symptoms of TMA 18 months post dasatinib treatment, and the second case [redacted] described a 71-year-old female who developed signs of TMA one year post dasatinib treatment. In both cases, the authors state that the diagnosis of TMA was confirmed by renal biopsy. Diagnosis of TMA is complex, the disease has multiple causes, and may mimic other clinical entities that commonly affect cancer patients. Diagnostic criteria are the presence of microangiopathic hemolytic anemia and thrombocytopenia without another apparent cause. Thus, the exclusion of other primary TMA syndromes may not be possible. An ADAMTS13 level, less than 10% of normal, supports a clinical diagnosis of an acquired TMA. The authors did not provide ADAMTS13 levels. The other two cases [redacted]had an insufficient information to draw a scientific conclusion. The remaining case [redacted] of a 71-year-old female with the diagnosis of CML reported a cascade of events like DIC, TLS, Streptococcal bacteremia, and invasive fungal infection. The events were confounded by the use of multiple drugs (dasatinib, daunoblastin, cytarabine, and methotrexate) and there was insufficient information in terms of concomitant medications and past medical history to make any causality assessment. A supplemental search of the corporate safety database for the interval from 28-Jun-2020 to 27-Jun-2021 with the PTs coded Disseminated intravascular coagulation, Haemolysis, Haemolytic uraemic syndrome, Microangiopathic hemolytic anemia, Scleroderma, Thrombotic microangiopathy (TMA), Thrombotic thrombocytopenic purpura, Microangiopathy, Autoimmune hemolytic anemia, Atypical hemolytic uraemic syndrome (MedDRA version 24.0), identified one serious and HCP confirmed literature post-marketing case ([redacted]) of a 48-year-old female who developed medically significant thrombotic microangiopathy while receiving dasatanib for CML. Dasatinib dose was increased three months into treatment and the patient developed worsening hypertension, nephrotic range proteinuria and hypoalbuminemia two months later. A kidney biopsy was compatible with renal-limited thrombotic microangiopathy induced by dasatinib. Urinalysis was unremarkable. The patient had no laboratory signs of microangiopathic hemolytic anemia and had not been on any other chemotherapy or targeted therapy. Dasatinib was withdrawn. The outcome of thrombotic microangiopathy was unknown. Based on the available information and biopsy results, the causality assessment of the reported event is considered possible. **Impact on the individual patient** TMA can cause significant morbidity or mortality. However, there are no quality of life data currently available from clinical trials evaluating the effects of TMA on individual patients. **Duration of treatment, risk period** TMA can occur at any time after treatment initiation. **Reversibility** May respond to plasma exchange or steroid administration.
Risk factors and risk groups	At the time of this report, there are no known risk groups or factors related to this potential risk specifically associated with dasatinib treatment.

Table 2.7.3.1-8: Important Identified Risk: Thrombotic Microangiopathy

Important Identified Risk Thrombotic Microangiopathy	
Preventability	Not preventable.
Impact on the risk-benefit balance of the product	TMA can cause significant morbidity or mortality. However, there are no quality of life data currently available from clinical trials evaluating the effects of TMA on individual patients.
Public health impact	None.
MedDRA terms	Thrombotic microangiopathy, Thrombotic thrombocytopenic purpura, Haemolytic uraemic syndrome, Microangiopathic haemolytic syndrome, Microangiopathic haemolytic anaemia, Microangiopathy and Atypical haemolytic uraemic syndrome.

Table 2.7.3.1-9: Important Potential Risk: Severe Hepatotoxicities

Important Potential Risk Severe Hepatotoxicities	
Potential mechanisms	Unknown
Evidence source and strength of evidence	Patients treated with dasatinib may be at increased risk of developing damage to the liver. Other drugs for CML treatment like dasatinib are known to cause liver damage. Patients with advanced phase CML or Ph+ ALL are more likely to show evidence of liver damage when on dasatinib. It is unknown if the damage was caused by the treatment or the leukaemia disease itself.
Characterization of risk	The listing included patients with at least 1 dose of dasatinib and excludes adverse events that started before study medication or more than 30 days after stop of study medication. The total number of patients treated with dasatinib in clinical trials included in this search was 5378. During the cumulative period, 22 patients were reported having experienced a grade of 3 or 4 severity event; there was only 1 grade 5 event reported with a preferred term of ascites. 11 of these patients were females and 12 were males. Most of the events were reported with a preferred term of ascites (n=13), either alone or in a context of fluid retention in other organs or concurrent with diarrhea or gastrointestinal infections. There was 1 case of hepatotoxicity and 4 reports of hepatocellular injury. However, most of these were reversible elevations of liver enzymes that resolved or did not lead to a fulminant course of liver failure, or were not related to study drug according to the investigator; the hepatic alterations occurred in the context of other comorbidities (i.e. severe infections, liver cyst infection, baseline disease progression) or other concomitant medications with liver hepatotoxic potential (i.e. asparaginase, acetaminophen, chemotherapy, itraconazole), or were related to baseline disease progression (i.e. progression of liver metastasis) In two cases from investigator sponsored research studies (and therefore not part of the BMS Clinical Trial Database), there was a history of viral hepatitis infection: one flare of hepatitis occurred in a patient with history of hepatitis

Table 2.7.3.1-9: Important Potential Risk: Severe Hepatotoxicities

Important Potential Risk Severe Hepatotoxicities	
	B, and one case of decompensated liver disease leading to death was reported in two patients with hepatitis C virus history. In one additional case, a patient had a history of Hepatitis B and in 2 cases, two patients had history of Hepatitis C, but these three patients only developed a reversible episode of ascites In conclusion, there were no cases of fulminant hepatitis attributable to dasatinib. There was a case of a patient necessitating a liver transplant after complication of a caesarean with infection of surgical site and liver failure, but this patient had stopped dasatinib several months before and was treated with imatinib during the last trimester of pregnancy
Risk factors and risk groups	No risk factors have been identified for subjects developing hepatic AEs with dasatinib. Severe hepatotoxicity is more common in advanced leukaemic disease and may be confounded by the disease itself.[39]
Preventability	Usually managed with dose reduction or interruption
Impact on the risk-benefit balance of the product	Severe hepatotoxicity appears to be a rare event in patients treated with dasatinib. There is no impact on risk-benefit balance of dasatinib administration.
Public health impact	None
MedDRA terms	Acquired hepatocerebral degeneration, Acute hepatic failure, Acute on chronic liver failure, Acute yellow liver atrophy, Ascites, Asterixis, Bacterascites, Biliary cirrhosis, PT Biliary fibrosis, Cardiohepatic syndrome, Cholestatic liver injury, Chronic hepatic failure, Coma hepatic, Cryptogenic cirrhosis, Diabetic hepatopathy, Drug-induced liver injury, Duodenal varices, Flood syndrome, Gallbladder varices, Gastric variceal injection, Gastric variceal ligation, Gastric varices, Gastric varices haemorrhage, Gastrooesophageal variceal haemorhage prophylaxis, Hepatectomy, Hepatic atrophy, Hepatic calcification, Hepatic cirrhosis, Hepatic encephalopathy, Hepatic encephalopathy prophylaxis, Hepatic failure, Hepatic fibrosis, Hepatic hydrothorax, Hepatic infiltration eosinophilic, Hepatic lesion, Hepatic necrosis, Hepatic steato-fibrosis, Hepatic steatosis, Hepatitis fulminant, Hepatobiliary disease, Hepatocellular foamy cell syndrome, Hepatocellular injury, Hepatopulmonary syndrome, Hepatorenal failure, Hepatorenal syndrome, Hepatotoxicity, Immune-mediated cholangitis, Immune-mediated hepatic disorder, Intestinal varices, Intestinal varices haemorrhage, Liver dialysis, Liver disorder, Liver injury, Liver operation, Liver transplant, Lupoid hepatic cirrhosis, Minimal hepatic encephalopathy, Mixed liver injury, Nodular regenerative hyperplasia, Non-alcoholic steatohepatitis, Non- cirrhotic portal hypertension, Nonalcoholic fatty liver disease, Oedema due to hepatic disease, Oesophageal varices haemorrhage, Peripancreatic varices, Portal fibrosis, Portal hypertension, Portal hypertensive colopathy, Portal hypertensive enteropathy, Portal hypertensive gastropathy, Portal vein cavernous transformation, Portal vein dilatation, Portopulmonary hypertension, Primary biliary cholangitis, Regenerative siderotic hepatic nodule, Renal and liver transplant, Retrograde portal vein flow, Raye's syndrome, Reynold's syndrome, Splenic varices, Splenic varices haemorrhage, Steatohepatitis, Subacute hepatic failure, Sugiura procedure, Varices oesophageal, Varicose veins of abdominal wall and White nipple sign. Acute graft versus host disease in liver, Allergic hepatitis, Alloimmune

Table 2.7.3.1-9: Important Potential Risk: Severe Hepatotoxicities

Important Potential Risk Severe Hepatotoxicities	
	hepatitis, Autoimmune hepatitis, Chronic graft versus host disease in liver, Chronic hepatitis, Graft versus host disease in liver, Hepatitis, Hepatitis acute, Hepatitis cholestatic, Hepatitis chronic active, Hepatitis chronic persistent, Hepatitis fulminant, Hepatitis toxic, Immune-mediated hepatitis, Ischaemic hepatitis,Lupus hepatitis, Non-alcoholic steatohepatitis, Radiation hepatitis, Steatohepatitis..

Table 2.7.3.1-10: Important Potential Risk: Direct Cardiotoxic Effect (eg, Cardiomyopathy)

Important Potential Risk Direct Cardiotoxic Effect (eg, Cardiomyopathy)	
Potential mechanisms	Unknown
Evidence source and strength of evidence	The cardiac adverse reactions of congestive heart failure/cardiac dysfunction, pericardial effusion, arrhythmias, palpitations, QT prolongation and myocardial infarction (including fatal) were reported in patients taking dasatinib. Cardiac adverse reactions were more frequent in patients with risk factors or a history of cardiac disease.
Characterisation of risk	Of the 2,182 patients with resistance or intolerance to prior imatinib therapy treated with dasatinib in clinical studies, CHF/cardiac dysfunction was reported as all Grades, 3%, Grade 3-5, 1.6%. In a multicentre, randomized, open-label Phase 3 study (CA180056) in 516 patients with newly diagnosed CP CML treated with either dasatinib or imatinib, CHF/cardiac dysfunction was reported for 7 (1.4%) and 1 (0.24%) subjects in the dasatinib and imatinib groups, respectively. Two cases in the dasatinib group and the 1 case in the imatinib treatment group were severe (Grade 3).[116] Echocardiograms were performed at baseline and after 3 months of study treatment. None of the subjects had a severe cardiac dysfunction with a left ventricular ejection fraction (LVEF) < 20% during the study. Among the 11 subjects with mild or moderate cardiac dysfunction, all except 1 (dasatinib-treated subject) had mild/moderate cardiac dysfunction at baseline and 7 of the 11 had baseline cardiac risk factors including prior MI, CHF, hyperlipidaemia, diabetes, or hypertension (4 dasatinib, 3 imatinib). The decline in LVEF from baseline was more common among dasatinib-treated subjects (4 subjects) than imatinib-treated subjects (2 subjects) recognizing that the number of subjects is small. Eight (8) of the 11 subjects with mild/moderate cardiac dysfunction remain on study treatment.[107] In addition, Table 2 of the dasatinib SmPC includes summary of relevant cardiac ADRs reported from 2,440 patients in clinical trials CML and Ph+ ALL (including 258 patients with newly diagnosed CP CML) in the System Organ Class (SOC) of Cardiac Disorders. In addition, information of fatal outcome for MI has been added. In a pooled paediatric population of 130 patients with CP-CML treated with dasatinib, CHF/cardiac dysfunction was reported in 3 (2.3%) patients. In a pooled population of 58 patients with AP/BP-CML, ALL or ALL treated with dasatinib, no AEs of CHF/cardiac dysfunction were reported.[132]

Table 2.7.3.1-10: Important Potential Risk: Direct Cardiotoxic Effect (eg, Cardiomyopathy)

Important Potential Risk Direct Cardiotoxic Effect (eg, Cardiomyopathy)	
	In a pooled paediatric population of 161 dasatinib in combination with chemotherapy treated paediatric patients (CA180372 and CA180204) with Ph+ ALL, CHF/cardiac dysfunction was reported in 1 (0.6%) subject (Grade 3-4).[130]
Risk factors and risk groups	The incidence of CHF increases with age. CHF incidence approaches 1% in patients over 65 years of age and approximately 75% of CHF cases have hypertension.[142] Several chemotherapy agents are associated with cardiotoxicities in other tumour types. Prior exposure to IFN-therapy or anthracyclines, pre-existing cardiac condition, and increasing age may all impact the risk of developing CHF. In CA180056 with 516 patients with newly diagnosed CP CML treated with either dasatinib or imatinib, while the protocol excluded subjects with significant recent cardiac events within 3 to 6 months prior to enrolment, nearly one quarter of the subjects had some degree of cardiac comorbidity. The most common cardiac comorbidities among randomized subjects were hypertension (dasatinib 13.5%, imatinib 13.1%), hyperlipidaemia (dasatinib 8.5%, imatinib 7.3%), diabetes (dasatinib 6.9%, imatinib 5.0%), and peripheral artery disease (dasatinib 2.7%, imatinib 1.5%). Cardiac events were more than twice as likely in subjects with cardiac comorbidity at baseline compared with subjects without cardiac comorbidity at baseline in both groups.[116] In a pooled paediatric population of 130 patients with CP-CML treated with dasatinib, CHF/cardiac dysfunction was reported in 3 (2.3%) patients. In a pooled population of 58 patients with AP/BP-CML, ALL or ALL treated with dasatinib, no AEs of CHF/cardiac dysfunction were reported.[132]
Preventability	It was usually managed with dose reduction or interruption. Subjects treated with dasatinib who have risk factors or a history of cardiac disease should be monitored carefully, and any subject with signs or symptoms consistent with cardiac dysfunction should be evaluated and treated.
Impact on the risk-benefit balance of the product	Severe hepatotoxicity appears to be a rare event with dasatinib. There are no quality of life data currently available from clinical trials evaluating effects of hepatotoxicity on individual patients.
Public health impact	Cardiac dysfunction (CHF) or myocardial infarction can cause significant morbidity or mortality. However, there are no quality of life data currently available from clinical trials evaluating effects of cardiotoxicity on individual patients.
MedDRA terms	Cardiac failure, Cardiomyopathy, Cardiac failure congestive, Cardiomyopathy acute, Congestive cardiomyopathy, Cytotoxic cardiomyopathy, Cardiac failure acute, Ventricular failure, Ventricular dysfunction, Cardiogenic shock, and Cardiopulmonary failure, Cardiac function diagnostic procedures, Cariomyopathies, Myocardial disorders NEC, Noninfectious myocarditis, Coronary artery disorders, Heart failure

Table 2.7.3.1-11: Important Potential Risk: Growth and Development Disorders and Bone Mineral Metabolism Disorders in Paediatric Population

Important Potential Risk Growth and Development Disorders and Bone Mineral Metabolism Disorders in Paediatric Population	
Potential mechanisms	Based on in vitro data, dasatinib may stimulate osteoblast differentiation leading to a direct increase in bone formation and results in dysregulation of bone remodelling. Dysregulated bone remodelling can result in osteoporosis. Clinical data supporting these potential mechanisms of action are not available. Mechanisms for hormonally related growth and development disorders are not known.
Evidence source and strength of evidence	Children with leukaemia who are receiving standard chemotherapy, radiation therapy or stem cell transplants are at increased risk for growth and development disorders and decreased bone mineralization as a result of their diagnosis and/or treatments.
Characterisation of risk	The Company conducted a cumulative search and review of the clinical database through 27-Jun-2014 on cases containing relevant MedDRA (v17.0) terms indicative of growth and development and bone disorders in the paediatric population (< 18 years of age). Adverse events associated with growth and development or bone disorders have been reported in a small proportion of subjects in the ongoing clinical trials. In the single agent setting (CA180018 and CA180226), 10/180 subjects reported 14 events regardless of relationship to study drug. In the multi-agent setting (CA180372), 13/101 subjects reported 14 events regardless of relationship to study drug. According to the treating investigators, 7 of the 28 events overall were considered related to therapy with dasatinib; these events were epiphyses delayed fusion, growth retardation, gynecomastia, osteoporosis and osteopenia. The completed Phase 1 clinical trial, CA180038, was not included because it used a dose range and schedule not consistent with the ongoing studies and the duration of treatment was generally short (<3 months in 33/38 subjects). The final CSR was issued 08-Dec-2009. A cumulative search and review of the Corporate safety database through 27-Jun-2014 revealed one additional case. Case [redacted] was received from the literature describing a female child who exhibited decreased growth velocity and growth hormone deficiency following therapy with imatinib and continuation of these events after transitioning to dasatinib therapy. One of identical female twins received treatment with imatinib for CML after several weeks of hydroxyurea treatment. The patient had received therapy with imatinib for 4 years and was transitioned to dasatinib (60 mg/m2) in an effort to achieve complete molecular remission. For the first 6 years of life, both twins were at the 95th percentile of height/age. Over the next 5 years, the height of the twin treated with TKI decreased to the 25th percentile, while her twin sister was unaffected and continued to grow at the 95th percentile of height/age. Nine months after starting dasatinib, she was still growing poorly and underwent detailed growth hormone (GH) testing with clonidine and arginine. The test revealed the patient had inappropriately low GH response following oral clonidine and IV arginine. The patient was diagnosed with growth hormone deficiency. [143] From the available data, the rate of growth and development disorders and bone mineral metabolism disorders in paediatric and adolescent subjects in

Table 2.7.3.1-11: Important Potential Risk: Growth and Development Disorders and Bone Mineral Metabolism Disorders in Paediatric Population

Important Potential Risk Growth and Development Disorders and Bone Mineral Metabolism Disorders in Paediatric Population	
	the settings under study appears very low. Monitoring for this potential risk continues in the ongoing clinical trials. A supplemental search of the Corporate safety database for the interval of 28-Jun-2014 to 27-Jun-2017 identified 10 cases with adverse events coding to the following PTs (MedDRA 20.0): Growth retardation (3 events; 2 non-serious and 1 serious), Osteonecrosis (2 serious events), Bone pain (3 events; 1 serious and 2 non-serious), Facial bone fractures (1 serious event). Case origination included clinical trial in 3 (CA180-372 in 2, CA180-226 in 1), solicited in 2 and spontaneously reported in 5 cases. These 10 cases describe 6 males and 4 females ranging in age from 6 years to 16 years (mean=11.1 years; n=10). Outcome was recovered/resolved in 2, not recovered/not resolved in 1 and unknown in 7. In a pooled paediatric population of 130 patients with CP-CML treated with dasatinib, bone growth and development AEs (any grade) were reported in 7 patients and drug related AEs were reported in 6 patients. The AEs reported were gynecomastia, growth retardation, epiphyses delayed fusion, osteopenia, and osteoporosis. In a pooled population of 58 patients with AP/BP-CML, ALL or ALL treated with dasatinib, 1 patient had a bone growth and development AE and it was not a drug-related AE.[132] In Studies CA180204 and CA180372, paediatric subjects treated with dasatinib were assessed for bone growth and development AEOSIs, and changes in height, weight, and BMI. Subjects were assessed annually while on study therapy and are to be followed for 5 years from the time the last subject discontinued the study therapy. All causality AEs associated with paediatric bone growth and development were reported in 9 (5.6%) out of 161 treated subjects, with osteopenia being the most frequent event (4 subjects, 2.5%). No subject had a Grade 3-4 event. Frequencies of bone growth and development AEs were comparable between subjects treated with continuous dasatinib (tablet only or any formulation) and the total population, and no subject treated with discontinuous dasatinib had an event. One subject (0.6%) among all treated subjects had a dasatinib-related Grade 1 paediatric bone growth and development AE of osteopenia.[130]
Risk factors and risk groups	Patients of pre-pubertal age may be at increased risk for any potential growth related effects. Paediatric patients with leukaemia or receiving standard chemotherapy, radiation therapy or stem cell transplants are at increased risk for growth and development disorders and decreased bone mineralization as a result of their diagnosis and/or treatments. It is unknown if treatment with dasatinib in this setting will alter this risk.
Preventability	Preventability measures are unknown. It is unknown if GH replacement therapy for children with CML or Ph+ ALL treated with TKIs is safe and thus this intervention is not considered at this time.
Impact on the risk-benefit balance of the product	With the limited data available, it is unknown if dasatinib therapy has an impact on an individual patient.
Public health impact	With the limited data available, it is unknown if dasatinib therapy has a potential public health impact on safety concern.

Table 2.7.3.1-11: Important Potential Risk: Growth and Development Disorders and Bone Mineral Metabolism Disorders in Paediatric Population

Important Potential Risk Growth and Development Disorders and Bone Mineral Metabolism Disorders in Paediatric Population	
MedDRA terms	Metabolic bone disorders (including PTs Osteopaenia, Osteoporosis, Osteolysis, Osteomalacias, and Osteodystrophy), Bone disorders NEC, Bone related signs and symptoms, Epiphyseal disorders; Bone and joint injuries, Fractures; Growth retardation

Table 2.7.3.1-12: Important Potential Risk: Toxic Skin Reactions

Important Potential Risk Toxic Skin Reactions	
Potential mechanisms	Potential immune-related cytotoxic reactions
Evidence source and strength of evidence	Toxic skin reactions are rare diseases. The annual incidence is 1.2-6.0 cases per million persons for Steven Johnson syndrome and 0.4-1.9 cases per million persons for toxic epidermal necrolysis.[144, 145] Infection (eg herpes simplex virus and mycoplasma pneumoniae) is the identified etiology for the majority of erythema multiforme (EM) cases. However, therapeutic drugs and immunizations have been associated with EM as well. Mild cases of EM resolve without sequelae and do not require treatment.[146] Based on the currently available information, these happen to be rare events with the use of dasatinib. Impact of the medication may be mild to very severe skin reactions. There have been 14 cases reported since the time dasatinib has been on market (Since Jun-2006) where patients experienced mild to severe form of skin reactions. Patients have been reported to recover once dasatinib was interrupted or stopped. Patients may receive fluids, electrolytes, mechanical supplementation and wound care in some cases for treatment of these skin reactions.
Characterisation of risk	Corporate safety database: A cumulative search and review of the safety database through 27-Jun-2014 was conducted on cases containing AEs/SAEs encoding to the following MedDRA PTs: EM, SJS, and TEN. This search included all HPC and non-HPC serious cases from completed and ongoing clinical trials and all HPC and non-HPC serious and nonserious cases from spontaneous, scientific literature, and phase 4/solicited cases. The search identified a total of 14 cases reporting the following relevant PTs: Erythema multiforme (EM, 7 cases), Stevens-Johnson syndrome (SJS, 6) and Toxic epidermal necrolysis (TEN,1). Of these 14 cases, 6 cases [redacted] were reported spontaneously, 5 cases [redacted], and [redacted] were received from investigator-sponsored clinical trials, 2 cases [redacted] and [redacted] were reported from a phase 4 trial and 1 case [redacted] was received from published scientific literature. In 11 of the 14 cases, patients received dasatinib for the treatment of the following conditions: CML (6) and ALL (5). For the remaining 3 cases, indication of use was not reported. A supplemental search of the Corporate safety database from 28-Jun-2014 to 27-Jun-2017 (using MedDRA 20.0) identified 7 additional cases, all assessed as serious (2 clinical trial, 2 spontaneous, 1 literature post-marketing and 1 solicited) reporting Erythema multiform in 4 cases [redacted]

Table 2.7.3.1-12: Important Potential Risk: Toxic Skin Reactions

Important Potential Risk Toxic Skin Reactions	[redacted], [redacted]) and Stevens-Johnson syndrome in 3 cases ([redacted], [redacted] Time to onset ranged from 7 days to 373 days (mean=190 days, n=2). Outcomes of the toxic skin events included recovered/resolved in 2, recovering/resolving in 1, not recovered/not resolved in 2 and unknown in 2. Clinical Database: Five skin reactions (0.18%; regardless of relationship) with investigator verbatim or preferred terms consistent with toxic skin reactions have been reported in dasatinib clinical trials in 2,712 study subjects in the approved indications. All with the exception of one case [redacted] TEN) were reported by investigators as nonserious AEs and are not included in the Corporate safety database.
Risk factors and risk groups	Patient groups most at risk for SJS and TEN include elderly adults, women, immunocompromised patients, and those with slow acetylator genotypes. A strong association between therapeutic drugs and development of cutaneous eruptions is observed in 80% of cases; however infections and immunizations have also been implicated in some cases.[144, 145] TEN is the most severe form of toxic skin reaction. The female-to-male ratio for TEN is 1.5:1.[147] TEN may occur in all age groups; however, the mean age of patients with TEN is reported to be between 46 and 63 years. Carbamazepine-induced TEN has been observed in HLA-B*1502–positive Han Chinese patients.[148] Based on these data, the US Food and Drug Administration recommends screening for the HLA-B*1502 allele before initiating carbamazepine in patients of Asian ancestry.[149] There is no genotype known to be associated with toxic skin reactions in dasatinib-treated patients.
Preventability	No clear prevention exists. However, once recognized, dasatinib should be interrupted or discontinued if appropriate to prevent progression to a more severe skin reaction. Treatment for severe events includes early admission for treatment with fluid, electrolyte, protein, and energy supplementation, mechanical ventilation, and wound care.[150]
Impact on the risk-benefit balance of the product	Toxic skin reactions appear to be rare events with dasatinib. The acute impact on an individual patient depends upon the nature and severity of the skin reaction. Longer term, the reaction may affect the ability of the patient to continue dasatinib therapy and may require changing to alternative cancer therapy. Whereas mild events such as grade 2 EM may have little impact on quality of life or the ability to tolerate dasatinib long-term, severe events may lead to immediate dasatinib discontinuation, life-threatening symptoms and hospital admission. There are no quality of life data currently available from clinical trials evaluating effects of toxic skin reactions on individual patients.
Public health impact	None
MedDRA terms	Erythema multiforme, Toxic epidermal necrolysis, and Stevens-Johnson syndrome

Table 2.7.3.1-13: Important Potential Risk: CYP3A4 Drug Interactions

Important Potential Risk CYP3A4 Drug Interactions	
Potential mechanisms	Dasatinib is primarily metabolised by the human CYP3A4 enzyme, is a significant inhibitor of CYP3A4, and is a weak inhibitor of all other major cytochrome P450 isozymes.
Evidence source and strength of evidence	Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. CYP3A4 substrates known to have a narrow therapeutic index (eg astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids [ergotamine, dihydroergotamine]) should be administered with caution in patients receiving dasatinib
Characterisation of risk	No cases of CYP3A4 drug interactions have been reported as AEs in the 2,712 study subjects in clinical trials in the approved indications. A cumulative search of the Corporate safety database through 27-Jun-2014 on cases reporting AEs/SAEs (MedDRA version 17) encoding to the PT "Drug Interactions" identified a total of 55 (45 HPC, 10 non-HPC) cases. Of these 55 cases, 16 cases (15 HPC and 1 non-HPC) encoded to the following search term: Drug interactions and CYP3A4 interacting drugs.[151] Of the above mentioned 16 cases, 12 were received from spontaneous sources, 3 from clinical trials and 1 case was received from phase 4/solicited studies. Age was reported in 11 cases and ranged from 18-years-old to 78-years-old (mean age=57-years-old and 1-month-old). The gender was provided in 15 cases (11 males, 4 females and 1 unknown). Of these 16 cases, 10 were reported as serious and 6 were reported as non-serious. For the remaining 39 cases, 32 were received from spontaneous sources, 3 from clinical trials, 3 cases were received from phase 4/solicited studies and 1 case was received from published scientific literature. Age was reported in 21 cases and ranged from 42-years-old to 78-years-old (mean age=54-years-old and 9-month-old). The gender was provided in 31 cases (13 males, 18 females and was reported as unknown in 3 cases and not reported in 5 cases). Of these 39 cases, 19 were reported as serious and 20 were reported as non-serious. A supplemental search of the Corporate safety database was performed for the interval of 28-Jun-2014 to 27-Jun-2017 for all cases reporting an adverse event coded to the PT Drug interaction (MedDRA 20.0). The search identified 38 cases (31 spontaneous cases [13 serious and 18 non-serious], 6 solicited cases [2 serious and 4 non-serious] and 1 case from the literature [serious]). Review of the cases indicated that 9 involved concomitant administration of a CYP3A4 inhibitor and 5 a CYP3A4 substrate. There was 1 fatal outcome ([redacted]) involving concomitant use of apixaban and lafutidine in a 74-year-old patient with CML who experienced upper gastrointestinal haemorrhage and later died due to cardiac failure.
Risk factors and risk groups	Co administration with dasatinib of CYP3A4 inhibitors, inducers, or substrates.[152,151]
Preventability	CYP3A4 drug interactions can be prevented by choosing alternative medications or adjusting the dasatinib dose as described above (see "Impact on the individual patient").
Impact on the risk-benefit balance of the product	Drugs co administered with dasatinib need to be carefully evaluated for potential CYP3A4-mediated interactions. The SmPC and USPI highlight several concerns and possible interventions:

Table 2.7.3.1-13: Important Potential Risk: CYP3A4 Drug Interactions

Important Potential Risk CYP3A4 Drug Interactions	
	Concomitant use of dasatinib and medicinal products that potently inhibit CYP3A4 may increase exposure to dasatinib, leading to a higher incidence of adverse events. Therefore, in patients receiving dasatinib, co administration of a potent CYP3A4 inhibitor is not recommended. If SPRYCEL must be administered with a strong CYP3A4 inhibitor, a dose decrease should be considered. Based on pharmacokinetic studies, a dose decrease to 20 mg daily should be considered for patients taking SPRYCEL 100 mg daily. For patients taking SPRYCEL 140 mg daily, a dose decrease to 40 mg daily should be considered. These reduced doses of SPRYCEL are predicted to adjust the area under the curve (AUC) to the range observed without CYP3A4 inhibitors. However, there are no clinical data with these dose adjustments in patients receiving strong CYP3A4 inhibitors. If SPRYCEL is not tolerated after dose reduction, either the strong CYP3A4 inhibitor must be discontinued, or SPRYCEL should be stopped until treatment with the inhibitor has ceased. When the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the SPRYCEL dose is increased. Concomitant use of dasatinib and medicinal products that induce CYP3A4 may substantially reduce exposure to dasatinib, potentially increasing the risk of therapeutic failure. Therefore, in patients receiving dasatinib, co administration of alternative medicinal products with less potential for CYP3A4 induction should be selected. If patients must be co administered a strong CYP3A4 inducer, based on pharmacokinetic studies, a SPRYCEL dose increase should be considered. If the dose of SPRYCEL is increased, the patient should be monitored carefully for toxicity Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. Therefore, caution is warranted when dasatinib is co administered with CYP3A4 substrates of narrow therapeutic index. The specific impact will depend upon the specific CYP3A4 substrate.
Public health impact	None
MedDRA terms	Drug interaction

Table 2.7.3.1-14: Important Potential Risk: Hepatitis B Virus (HBV) Reactivation

Important Potential Risk Hepatitis B Virus (HBV) Reactivation	
Potential mechanisms	The precise mechanism for this AE is unknown, but it most likely has to do with poorly characterised immunosuppresive effects of BCR-ABL TKIs
Evidence source and strength of evidence	Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome
Characterisation of risk	No definitive cases of HBV reactivation were reported as AEs in over 3,000 study subjects in clinical trials of dasatinib. Five cases were identified in which a reactivation of HBV may have been reported, but a lack of baseline serology and HBV DNA levels makes these cases speculative. A frequency and relevant numerator/denominator for HBV reactivation cannot be determined because HBV serology was not a requirement for study entry and therefore, the number of patients at risk for HBV reactivation is unknown.

Table 2.7.3.1-14: Important Potential Risk: Hepatitis B Virus (HBV) Reactivation

Important Potential Risk Hepatitis B Virus (HBV) Reactivation	
	A comprehensive, cumulative search of the corporate safety database through 19-Feb-2016 was performed to identify all spontaneous, clinical trial and literature cases in which dasatinib was considered a suspect or interacting drug and at least one of the reported adverse event terms in the case was mapped to PT containing the phrase "Hepatitis B" using MedDRA Version 18.1. Seven unique cases were identified. Four cases were consistent with HBV reactivation and in the other 3 cases it was unclear if a reactivation or a new case of HBV infection were being reported. A supplemental search of the Corporate safety database for the interval of 20-Feb-2016 to 27-Jun-2017 for the PTs Hepatitis B or Hepatitis B reactivation (MedDRA 20.0) retrieved 2 medically significant cases: (both originating from the same post-marketing literature article).
Risk factors and risk groups	Patients who have positive HBV serology at baseline are at risk of reactivation of HBV infection.
Preventability	Reactivations can be prevented by assessing for baseline HBV infection and initiating preventative therapy with an HBV active nucleoside or nucleotide analogue
Impact on the risk-benefit balance of the product	HBV reactivations can be associated with hepatic failure, death, or hepatic transplantation. In addition, it may be necessary to interrupt dasatinib therapy while the HBV reactivation is being diagnosed and treated.
Public health impact	None
MedDRA terms	Hepatitis B

2.7.3.2 *Presentation of the Missing Information*

Table 2.7.3.2-1: Missing Information

Missing Information	
Population in need of further characterisation:	
Paediatric data: Children < 1 year of age	There is no experience with SPRYCEL treatment in children under 1 year of age
Reproductive and lactation data	There are limited data on the risk of dasatinib in pregnancy and the risk to a baby if a mother on dasatinib breast feeds. However, due to birth defects and other problems in babies born to mothers who took dasatinib during pregnancy, it is recommended that women taking dasatinib do not become pregnant or breast-feed.
Anticipated risk/consequence of the missing information:	
Carcinogenicity	Patients in dasatinib studies could not have a recent second cancer so the effect of dasatinib on the growth of another cancer discovered either before, during, or after stopping dasatinib is not known.

2.8 Summary of the Safety Concerns

Safety concerns are summarized in Table 2.8-1.

Table 2.8-1: Summary of Safety Concerns

Important identified risks	Myelosuppression Fluid Retention Bleeding Related Events QT Prolongation PAH Pregnancy Related Malformative or Foeto/ Neonatal Toxicity Nephrotic Syndrome Thrombotic Microangiopathy
Important potential risks	Severe Hepatotoxicities Direct Cardiotoxic Effects (eg, Cardiomyopathy) Growth and development disorders and bone mineral metabolism disorders in the paediatric population Toxic Skin Reactions CYP3A4 Drug Interactions HBV Reactivation
Missing information	Carcinogenicity Paediatric data • Children < 1 year of age Reproductive and lactation data

3 PART III: PHARMACOVIGILANCE PLAN

The objective of the PhV plan is to proactively identify and characterize all safety concerns that have been identified or have potential to be associated with the use of dasatinib. The ongoing activities involve comprehensive approach to case and aggregate data assessment and signal detection to identify potential new risks, and continuously evaluate and monitor for known identified and potential safety risks. The safety assessments included in the following sections are key elements that are part of a cohesive PhV plan that will inform of risks and risk mitigation strategies for events of special interest. The risk minimisation plan is outlined in Section 5.

3.1 Routine Pharmacovigilance Activities

See Annex 4 for forms, as applicable, summarized in Table 3.1-1.

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are summarized in Table 3.1-1

Table 3.1-1: Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection

Specific adverse reaction follow-up questionnaires	
Specific adverse reaction follow-up questionnaires for PAH	Use of the Dasatinib Pulmonary Hypertension (PH) Follow-Up Questionnaires (See Annex 4) to collect additional clinical and diagnostic information on reported PAH during dasatinib exposure in order to characterise the event and outcomes.
Specific adverse reaction follow-up questionnaires for HBV Reactivation	Adverse event report questionnaire will systematically collect targeted clinical and treatment information for individual case safety reports (See Annex 4).
Other forms of routine pharmacovigilance activities for:	
Direct cardiotoxic effects	Targeted follow-up efforts for individual case safety reports of relevant serious cardiac events (eg, CHF, cardiomyopathy, myocardial ischemic events) to collect additional clinical and diagnostic information and to provide comprehensive data assessment and reporting in the PSUR/PBRER.
Growth and development disorders and bone mineral metabolism disorders in paediatric patients	Long-term safety assessments with follow up plan for 5 years after completing study treatment in CML and Ph+ ALL paediatric studies (CA180018, CA180204, CA180226, and CA180372) for clinical evaluation of disorder of growth and development and of bone mineral metabolism in paediatric patients. In Study CA180226, early long-term growth and development assessments for subjects on treatment in Cohort 3 who were < 11 years old when enrolled, will continue until subjects are 18 years old.

3.2 Additional Pharmacovigilance Activities

None.

3.3 Summary Table of Additional Pharmacovigilance Activities

None.

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

None.

5 PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

5.1 Routine Risk Minimisation Measures

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Safety Concern: Myelosuppression	**Routine risk communication:** The SmPC warns of the risk of myelosuppression in Section 4.4, and Section 4.8 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Specific guidance on myelosuppression monitoring and management including adjustment guidelines based on defined neutropaenia and thrombocytopaenia endpoints in Sections 4.2 and 4.4 and 4.8 as appropriate. **Other routine risk minimisation measures beyond the Product Information:** SPRYCEL is a medicinal product subject to restricted medical prescription and is used primarily by haematologists/oncologists experienced in the treatment of leukaemia and familiar with the management of myelosupression
Safety Concern: Fluid Retention	**Routine risk communication:** The SmPC warns of the risk of fluid retention and related conditions (pericardial effusion, pulmonary oedema, severe ascites and generalized oedema) in Section 4.4 and Section 4.8. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Specific guidance on specific risk, management and reversibility of fluid retention based on clinical trial experience in Sections 4.2. **Other routine risk minimisation measures beyond the Product Information**: None
Safety Concern: Bleeding Related Events	**Routine risk communication:** The SmPC warns of the risk of bleeding related events in Section 4.4 and Section 4.8.

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Specific guidance on specific risk, management and reversibility of bleeding related events based on clinical trial experience in Sections 4.2. **Other routine risk minimisation measures beyond the Product Information:** None
Safety Concern: QT Prolongation	**Routine risk communication:** The SmPC warns of the risk of QT prolongation in Section 4.4 and Section 4.8. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information**: None
Safety Concern: Pregnancy Related Malformative or Foeto/ Neonatal Toxicity	**Routine risk communication**: The SmPC warns of the risk of pregnancy related malformative or foeto/ neonatal toxicity in Section 4.4, Section 4.6, and Section 5.3. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Specific guidance on fertility, pregnancy and lactation in Section 4.6. **Other routine risk minimisation measures beyond the Product Information:** None
Safety Concern: Pulmonary Arterial Hypertension	**Routine risk communication**: The SmPC warns of the risk of pulmonary arterial hypertension (PAH) in Section 4.4 and Section 4.8. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Specific guidance for dose withholding and permanent discontinuation in the event of suspect or diagnosed PAH; co-medication and co-morbidity, interventions and outcome in Section 4.4. **Other routine risk minimisation measures beyond the Product Information:** None
Safety Concern: Nephrotic Syndrome	**Routine risk communication**: The SmPC warns of the risk of nephrotic syndrome in Section 4.8. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Safety Concern:	**Routine risk communication:**

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Thrombotic Microangiopathy	The SmPC warns of the risk of thrombotic microangiopathy in Sections 4.4 and 4.8. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Specific guidance for dose withholding and permanent discontinuation in the event of thrombotic microangiopathy is described in SmPC Section 4.4. **Other routine risk minimisation measures beyond the Product Information:** None.
Safety Concern: Severe Hepatotoxicities	**Routine risk communication**: The SmPC warns of the risk of severe hepatotoxicities in Section 4.4, Section 4.8 and Section 5.2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Safety Concern: Direct Cardiotoxic Effects (eg, Cardiomyopathy)	**Routine risk communication**: The SmPC warns of the risk of direct cardiotoxic effects (eg, cardiomyopathy) in Section 4.2, Section 4.4 and Section 4.8. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Safety Concern: Growth and Development or Bone disorders	**Routine risk communication**: The SmPC warns of the risk of growth and development disorders in Sections 4.4 and 4.8. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Safety Concern: Toxic Skin reactions	**Routine risk communication**: The SmPC warns of the risk of toxic skin reactions in Section 4.8. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Safety Concern: CYP3A4 Drug Interactions	**Routine risk communication**: The SmPC warns of the risk of CYP3A4 drug interactions in Section 4.4, 4.5 and 4.8. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None

Table 5.1-1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: None
Safety Concern: HBV Reactivation	**Routine risk communication:** The SmPC warns of the risk of HBV reactivation in Section 4.4 and 4.8. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Safety Concern: Carcinogenicity	**Routine risk communication:** The SmPC warns of the risk of carcinogenicity in Section 5.3. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Safety Concern: Paediatric data: Children <1 year of age	**Routine risk communication:** The SmPC warns that there is no experience with SPRYCEL treatment in children under 1 year of age in Section 4.2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None
Safety Concern: Reproductive and lactation data	**Routine risk communication:** The SmPC warns of safety and efficacy of dasatinib in reproductive and lactation data in Sections 4.6 and 5.3. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None

5.2 Additional Risk Minimisation Measures

Additional risk minimisation measures are provided in Table 5.1-1. Details of proposed additional risk minimisation activities are provided in Annex 6.

Table 5.2-1: Additional Risk Minimisation Measures

Additional Risk Minimisation Direct Healthcare Professional Communication (DHPC)	**Objectives:** To minimize the occurrence, and mitigate the impact of HBV Reactivation by providing adequate warnings and information. **Rationale for the additional risk minimisation activity:** Need to screen patients for hepatitis B virus before treatment due to the potential risk of hepatitis B reactivation

Table 5.2-1: Additional Risk Minimisation Measures

	Target audience and planned distribution path: Healthcare professionals. The MAH must agree to the content and format of the educational material, together with a communication plan, with the national competent authority in each Member State prior to distribution in their territory (dissemination completed in the EEA Apr-2016). **Plans to evaluate the effectiveness of the interventions and criteria for success:** Results of routine PhV to assess the frequency and severity of HBV reactivation. Monitoring and documenting of safety findings in required aggregate reports. The results will be reported in PBRERs.

5.3 Summary Table of Risk Minimisation Measures

A summary of risk minimisation measures is provided in Table 5.3-1.

Table 5.3-1: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Myelosuppression	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4 and 4.8 SPRYCEL is a medicinal product subject to restricted medical prescription. Used primarily by haematologists/oncologists experienced in the treatment of leukaemia and familiar with the management of myelosupression	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
Fluid Retention	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4 and 4.8.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
Bleeding Related Events	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4 and 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None

Table 5.3-1: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
QT Prolongation	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
Pregnancy Related Malformative or Foeto/ Neonatal Toxicity	**Routine risk minimisation measures:** SmPC Sections 4.4, 4.6 and 5.3	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
Pulmonary Arterial Hypertension	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.8.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Dasatinib Pulmonary Hypertension (PH) Follow-Up Questionnaires (See Annex 4)
	Additional risk minimisation measures: None.	**Additional pharmacovigilance activities:** None
Nephrotic Syndrome	**Routine risk minimisation measures:** SmPC Section 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
Thrombotic Microangiopathy	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None

Table 5.3-1: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Severe Hepatotoxicities	**Routine risk minimisation measures:** SmPC Sections 4.4, 4.8 and 5.2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
Direct Cardiotoxic effects (e.g, cardiomyopathy)	**Routine risk minimisation measures:** SmPC Sections 4.2, 4.4, and 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up efforts for individual case reports of relevant serious cardiac events (eg, CHF, cardiomyopathy, myocardial ischemic events) to collect additional clinical and diagnostic information and to provide comprehensive data assessment and reporting in PSUR
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
Growth and Development Disorders and Bone Mineral Metabolism Disorders	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Long-term safety assessments with follow up plan for 5 years after completing study treatment in CML and Ph+ ALL paediatric studies (CA180018, CA180204, CA180226, and CA180372) for clinical evaluation of disorder of growth and development and of bone mineral metabolism in paediatric patients. In Study CA180226, early long-term growth and development assessments for subjects on treatment in Cohort 3 who were < 11 years old when enrolled, will continue until subjects are 18 years old.
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None

Table 5.3-1: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Toxic skin reactions	**Routine risk minimisation measures:** SmPC Section 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
CYP3A4 Drug interactions	**Routine risk minimisation measures:** SmPC Sections 4.4, 4.5, and 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
HBV Reactivation	**Routine risk minimisation measures:** SmPC Sections 4.4, and 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaires for HBV Reactivation (See Annex 4)
	Additional risk minimisation measures: DHPC issued in EU Apr-2016	**Additional pharmacovigilance activities:** None
Carcinogenicity	**Routine risk minimisation measures:** SmPC Section 5.3	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
Paediatric data: Children < 1 year of age	**Routine risk minimisation measures:** SmPC Section 4.2.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None
Reproductive and lactation data	**Routine risk minimisation measures:** SmPC Sections 4.6 and 5.3	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal**

Table 5.3-1: Summary of Risk Minimisation Measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		detection: None
	Additional risk minimisation measures: None	**Additional pharmacovigilance activities:** None

6 SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for SPRYCEL (dasatinib)

This is a summary of the risk management plan (RMP) for SPRYCEL. The RMP details important risks of SPRYCEL, how these risks can be minimise, and how more information will be obtained about SPRYCEL's risks and uncertainties (missing information).

SPRYCEL 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how SPRYCEL should be used.

This summary of the RMP for SPRYCEL should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of SPRYCEL's RMP.

I. The medicine and what it is used for

SPRYCEL is authorised for use in adults with newly diagnosed Philadelphia chromosome-positive (Ph+) Chronic Myeloid Leukaemia (CML) in Chronic Phase (CP); adults with CP, Accelerated Phase (AP), or Blast Phase (BP) CML with resistance or intolerance to prior therapy including imatinib; and Ph+ Acute Lymphoblastic Leukaemia (ALL) and lymphoid BP CML with resistance or intolerance to prior therapy. (see SmPC for the full indication). SPRYCEL is authorised for use in paediatric patients with newly diagnosed Ph+ CML in CP, or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib. It contains dasatinib as the active substance and it is given orally by tablet or powder for oral suspension (PFOS).

Further information about the evaluation of SPRYCEL's benefits can be found in SPRYCEL's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000709/human_med_001062.jsp&mid=WC0b01ac058001d124.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of SPRYCEL, together with measures to minimise such risks and the proposed studies for learning more about SPRYCEL's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks

Together, these measures constitute *routine risk minimisation* measures.

In the case of SPRYCEL, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of SPRYCEL is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of SPRYCEL are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of SPRYCEL. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	Myelosuppression
	Fluid Retention
	Bleeding Related Events
	QT Prolongation
	PAH
	Pregnancy Related Malformative or Foeto/ Neonatal Toxicity
	Nephrotic Syndrome
	Thrombotic Microangiopathy

List of important risks and missing information

Important potential risks	Severe Hepatotoxicities Direct Cardiotoxic Effects (eg, Cardiomyopathy) Growth and development disorders and bone mineral metabolism disorders in the paediatric population Toxic Skin Reactions CYP3A4 Drug Interactions HBV Reactivation
Missing information	Carcinogenicity Paediatric data • Children < 1 year of age Reproductive and lactation data

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important identified risks

Myelosuppression	
Evidence for linking the risk to the medicine	Treatment with dasatinib is associated with anaemia, neutropaenia and thrombocytopaenia. Their occurrence is disease phase dependent and is more frequent in patients with advanced phase CML or Ph+ ALL than in CP CML. Myelosuppression is generally reversible and usually managed by withholding dasatinib temporarily and/or dose reduction.
Risk factors and risk groups	The risk of myelosuppression is dose dependent. Myelosuppression is more frequent in patients with advanced phase CML or Ph+ ALL than in CP CML. Other risk factors: hepatic impairment (≥ Grade 2 alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin), CYP3A4 inhibitors, preexisting myelosuppression, prior imatinib treatment and chemotherapy, underlying haematologic malignancies.
Risk minimisation measures	SmPC Sections 4.2, 4.4 and 4.8 SPRYCEL is a medicinal product subject to restricted medical prescription
Fluid Retention	
Evidence for linking the risk to the medicine	Dasatinib may cause various types of fluid retention. Fluid around the lining of the lung (pleural effusion) or heart (pericardial effusion), or fluid in the lungs (pulmonary oedema) may cause shortness of breath. Fluid in the abdomen (ascites) can cause abdominal discomfort or shortness of breath. Fluid under the skin (superficial oedema) can occur in various places in the body and may cause swelling or discomfort.
Risk factors and risk groups	Risk factors include older age, fluid retention at baseline, prior imatinib treatment, and renal impairment. While the safety profile of dasatinib in the elderly population was generally similar to that in the younger population, the incidence of

Important identified risks

	pleural effusion increases with age. For example, patients aged 65 years and older are more likely to experience fluid retention events and should be monitored closely.
Risk minimisation measures	SmPC Sections 4.2, 4.4 and 4.8.
Bleeding Related Events	
Evidence for linking the risk to the medicine	Bleeding has been very common in studies with dasatinib affecting more than 1 out of every 10 patients and can occur in any part of the body such as the brain, stomach or intestines. Severe and life-threatening or fatal bleeding has occurred.
Risk factors and risk groups	Patients with leukaemia, severe thrombocytopaenia, coagulation disorder, cardiovascular disorders, and patients who take medicinal products that inhibit platelet function or anticoagulants. Most bleeding related events in these patients were typically associated with grade 3 or 4 thrombocytopaenia CNS haemorrhage is a known complication of leukaemia and, like GI haemorrhage, typically results from severe thrombocytopaenia or platelet dysfunction. GI haemorrhage is a known comorbid condition in an acutely ill population of Leukaemic patients, typically resulting from thrombocytopaenia or platelet dysfunction. Among these subjects without significant thrombocytopaenia, the frequency of haemorrhage events was similar between the dasatinib and imatinib groups (any grade: 9.4% vs 9.1%; Grade 3 to 4: 1.8% vs 1.5%). There was a trend toward more frequent "other" (defined as ear haemorrhage, epistaxis, gingival bleeding, haematoma, haematuria, haemoptysis, petechiae, and scleral haemorrhage) haemorrhage events with imatinib (dasatinib: 6.4%, imatinib: 8.1%). These data suggest that among subjects with adequate platelet counts for normal hemostasis, bleeding events were infrequent and low grade among both treatment groups.
Risk minimisation measures	SmPC Sections 4.2, 4.4 and 4.8
QT Prolongation	
Evidence for linking the risk to the medicine	Dasatinib may increase the risk of prolongation of QTc in patients including those with hypokalaemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking antiarrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy.
Risk factors and risk groups	Patients with hypokalaemia or hypomagnesaemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicinal products or other medicinal products which lead to QT prolongation, and cumulative high dose anthracycline therapy. Other risk factors include baseline QT prolongation, cardiac history (eg, CHF, bradycardia, MI), elderly, and female.
Risk minimisation measures	SmPC Sections 4.4 and 4.8
Pulmonary Arterial Hypertension (PAH)	

Important identified risks

Evidence for linking the risk to the medicine	Dasatinib may increase the risk of developing pulmonary arterial hypertension (PAH) which may occur any time after initiation, including after more than 1 year of treatment. Manifestations include dyspnea, fatigue, hypoxia, and fluid retention. PAH may be reversible on discontinuation of dasatinib.
Risk factors and risk groups	The cumulative search through 27-Jun-2013, provided the following information on each risk group/risk factor: **Gender and age:** As with all post-marketing the reporting age and gender of patients was not reported in all cases. Gender was provided in 75 of the reported 86 cases of PAH (35 males, and 40 females). Age and gender was provided in all 39 cases of catheter confirmed PAH. In the catheter confirmed PAH group, 25 of the 39 reported cases were female. The median age of patients was slightly lower in the catheter confirmed PAH group when compared to the total group. Of note, the median age of subjects enrolled in the clinical trial program in second line therapy is 56 years. The median age of patients with catheter confirmed PAH was 53 years. **Underlying disease:** The majority of patients receiving dasatinib were being treated for CML or ALL per the licensed indications, although occasional cases of solid tumours were reported with PH from other clinical trials with dasatinib. A single literature report of PAH associated with dasatinib use in metastatic malignant melanoma is the only report of off label use and PAH. **Prior medical history:** Of the 39 subjects with catheter confirmed PAH, 5 had prior medical histories of fluid retention events (pleural effusion, generalized oedema) reported with dasatinib or prior TKI treatment before the episode of PAH. An additional 10 had significant medical history of relevant serious cardiovascular-pulmonary disease including miliary tuberculosis (TB) (2), coronary artery disease requiring coronary stenting (2), myocardial infarct (1), angina (1), hypertension (1), heavy smoking (1), femoral thrombosis (1) and chronic obstructive pulmonary disease (1). **Time to onset:** Of the 86 cases of reported PAH (catheter confirmed and otherwise), the time to onset was reported in 58 cases. The time to onset of reported PAH after the initiation of treatment with dasatinib in these 58 cases ranged from 0.06 months to 84 months (mean = 30 months). The time to onset after the initiation of treatment with dasatinib in the PAH cases confirmed by RHC ranged from 0.26 months to 75 months (mean = 29 months). The interval search (28-June 2013 to 27-June 2014) provided the following information on each risk group/risk factors: **Gender and age:** Gender was reported in 25 of the 35 cases of PAH (11 males and 14 females). Age was reported in 25 cases. In these cases, the mean age was 55.6 years (range 16-73 years). **Underlying disease:** Of the 35 cases with reported PAH, all but 2 were reported as being treated for CML or ALL per the licensed indications. In one case, the indication was not reported, and a single spontaneous report of PAH associated with dasatinib use in metastatic malignant melanoma was the only report of off label use in these cases. **Prior medical history:** Of the 35 patients with PAH, several cases had relevant pre-existing or co-morbid cardiopulmonary or connective tissue disease, including preexisting arterial hypertension (9), pre-existing cardiac

Important identified risks

	valvular disease (2), atrial fibrillation (2), including 1 with cardiomegaly, scleroderma (1), chronic obstructive pulmonary disease (1), pneumonia legionella (1), smoking history (3), sleep apnoea (2), and pulmonary tuberculosis (1). **Time to onset**: Time to onset of PAH after initiation with dasatinib treatment was reported in 20 of the 35 cases. The time to onset in these cases ranged from 0.33- 66 months (mean = 29.5 months).
Risk minimisation measures	SmPC Sections 4.4 and 4.8.
Pregnancy Related Malformative or Foeto/ Neonatal Toxicity	
Evidence for linking the risk to the medicine	Based on limited human data, dasatinib can cause foetal harm when administered to a pregnant woman. Adverse pharmacologic effects of dasatinib including hydrops fetalis, foetal leukopenia, and foetal thrombocytopenia have been reported with maternal exposure to dasatinib Advise females of reproductive potential to avoid pregnancy, which may include the use of effective contraception, during treatment with dasatinib and for 30 days after the final dose
Risk factors and risk groups	**Female Partners of Male Patients**: Seven of the 82 cases confirmed that the female partner and/or male patient, did not use any form of contraception at the time of conception. Additionally, only 4 cases provided details on contraception use, described as double barrier contraception and condoms (2 cases each). **Female Patients**: Five of the 104 cases confirmed that the female partner and/or male patient, did not use any form of contraception at the time of conception. Additionally, 23 cases provided details on contraception use as the following: oral contraception (9), abstinence, condoms (3 each), barrier method, unspecified contraception (2 each), and abstinence/condom, contraception via temperature measurement, intramuscular contraceptive, and "safe periods" (1 each).
Risk minimisation measures	SmPC Sections 4.4, 4.6 and 5.2
Nephrotic Syndrome	
Evidence for linking the risk to the medicine	Nephrotic syndrome is a constellation of clinical and laboratory features of renal disease. Symptoms and signs include heavy proteinuria (protein excretion greater than 3.5 g/24hours), hypoalbuminemia (less than 3 g/dL), and peripheral oedema. Although untreated or unrecognized Nephrotic Syndrome may be a serious condition, the symptoms, signs and laboratory abnormalities (peripheral oedema, proteinuria and hypoalbuminuria) are easily recognized by trained medical providers.
Risk factors and risk groups	At the time of this report there were no known risk groups or factors related to this potential risk specifically associated with dasatinib treatment.
Risk minimisation measures	SmPC Section 4.8
Thrombotic Microangiopathy	
Evidence for linking the risk to the medicine	George, JN, Nester, CM Martino et al Mittal et al Corporate Safety Database.

Important identified risks

Risk factors and risk groups	At the time of this report, there are no known risk groups or factors related to this potential risk specifically associated with dasatinib treatment.
Risk minimisation measures	SmPC Sections 4.4 and 4.8

Important potential risks

Severe Hepatotoxicities	
Evidence for linking the risk to the medicine	Patients treated with dasatinib may be at increased risk of developing damage to the liver. Other drugs for CML treatment like dasatinib are known to cause liver damage. Patients on dasatinib have had damage to the liver develop. Patients with advanced phase CML or Ph+ ALL are more likely to show evidence of liver damage when on dasatinib. It is unknown if the damage was caused by the treatment or the leukaemia disease itself.
Risk factors and risk groups	No risk factors have been identified for subjects developing hepatic AEs with dasatinib. Severe hepatotoxicity is more common in advanced leukaemic disease and may be confounded by the disease itself.
Risk minimisation measures	SmPC Sections 4.4, 4.8 and 5.3

Direct Cardiotoxic Effect (eg, Cardiomyopathy)	
Evidence for linking the risk to the medicine	The cardiac adverse reactions of congestive heart failure/cardiac dysfunction, pericardial effusion, arrhythmias, palpitations, QT prolongation and myocardial infarction (including fatal) were reported in patients taking dasatinib. Cardiac adverse reactions were more frequent in patients with risk factors or a history of cardiac disease.
Risk factors and risk groups	The incidence of CHF increases with age. CHF incidence approaches 1% in patients over 65 years of age and approximately 75% of CHF cases have hypertension. Several chemotherapy agents are associated with cardiotoxicities in other tumour types. Prior exposure to IFN-therapy or anthracyclines, pre-existing cardiac condition, and increasing age may all impact the risk of developing CHF. In CA180056 with 516 patients with newly diagnosed CP CML treated with either dasatinib or imatinib, while the protocol excluded subjects with significant recent cardiac events within 3 to 6 months prior to enrolment, nearly one quarter of the subjects had some degree of cardiac comorbidity. The most common cardiac comorbidities among randomized subjects were hypertension (dasatinib 13.5%, imatinib 13.1%), hyperlipidaemia (dasatinib 8.5%, imatinib 7.3%), diabetes (dasatinib 6.9%, imatinib 5.0%), and peripheral artery disease (dasatinib 2.7%, imatinib 1.5%). Cardiac events were more than twice as likely in subjects with cardiac comorbidity at baseline compared with subjects without cardiac comorbidity at baseline in both groups.
Risk minimisation measures	SmPC Sections 4.2, 4.4, and 4.8

Growth and Development Disorders and Bone Mineral Metabolism Disorders in Paediatric Population

Important potential risks

Evidence for linking the risk to the medicine	Children with leukaemia who are receiving standard chemotherapy, radiation therapy or stem cell transplants are at increased risk for growth and development disorders and decreased bone mineralization as a result of their diagnosis and/or treatments.
Risk factors and risk groups	Patients of pre-pubertal age may be at increased risk for any potential growth related effects. Paediatric patients with leukaemia or receiving standard chemotherapy, radiation therapy or stem cell transplants are at increased risk for growth and development disorders and decreased bone mineralization as a result of their diagnosis and/or treatments. It is unknown if treatment with dasatinib in this setting will alter this risk.
Risk minimisation measures	SmPC Section 4.8

Toxic Skin Reactions

Evidence for linking the risk to the medicine	Toxic skin reactions are rare diseases. The annual incidence is 1.2- 6.0 cases per million persons for Steven Johnson syndrome and 0.4 - 1.9 cases per million persons for toxic epidermal necrolysis. Infection (eg herpes simplex virus and mycoplasma pneumoniae) is the identified etiology for the majority of erythema multiforme (EM) cases. However, therapeutic drugs and immunizations have been associated with EM as well. Mild cases of EM resolve without sequelae and do not require treatment Based on the currently available information, these happen to be rare events with the use of dasatinib. Impact of the medication may be mild to very severe skin reactions. There have been 14 cases reported since the time dasatinib has been on market (Since Jun-2006) where patients experienced mild to severe form of skin reactions. Patients have been reported to recover once dasatinib was interrupted or stopped. Patients may receive fluids, electrolytes, mechanical supplementation and wound care in some cases for treatment of these skin reactions.
Risk factors and risk groups	Patient groups most at risk for SJS and TEN include the elderly, women, immunocompromised, and those with slow acetylator genotypes. A strong association between therapeutic drugs and development of cutaneous eruptions is observed in 80% of cases; however infections and immunizations have also been implicated in some cases. TEN is the most severe form of toxic skin reaction. The female-to-male ratio for TEN is 1.5:1. TEN may occur in all age groups; however, the mean age of patients with TEN is reported to be between 46 and 63 years. Carbamazepine-induced TEN has been observed in HLA-B*1502–positive Han Chinese patients. Based on these data, the US Food and Drug Administration recommends screening for the HLA-B*1502 allele before initiating carbamazepine in patients of Asian ancestry. There is no genotype known to be associated with toxic skin reactions in dasatinib-treated patients.
Risk minimisation measures	SmPC Section 4.8

Important potential risks

CYP3A4 Drug Interactions	
Evidence for linking the risk to the medicine	Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. CYP3A4 substrates known to have a narrow therapeutic index (eg astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids [ergotamine, dihydroergotamine]) should be administered with caution in patients receiving dasatinib
Risk factors and risk groups	Co administration with dasatinib of CYP3A4 inhibitors, inducers, or substrates.
Risk minimisation measures	SmPC Sections 4.4, 4.5, and 4.8
HBV Reactivation	
Evidence for linking the risk to the medicine	Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome
Risk factors and risk groups	Patients who have positive HBV serology at baseline are at risk of reactivation of HBV infection.
Risk minimisation measures	SmPC Sections 4.4, and 4.8 Direct Healthcare Professional Communication (DHPC) issued in EU on 11-Apr-2016

Missing information

Carcinogenicity	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.3
Paediatric data: Children <1 year of age	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2
Reproductive and lactation data	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation of SPRYCEL.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for SPRYCEL.

7 LIST OF ABBREVIATIONS

Term	Definition
ADR	Adverse drug reaction
AE	Adverse event

Term	Definition
ALL	Acute lymphoblastic leukaemia
ALT	Alanine aminotransferase
AML	Acute myelogenous leukaemia
AP	Accelerated phase
APD	Action Potential Duration
AR	Adverse reaction
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the curve
BID	Twice daily
BMD	Bone mineral density
BMS	Bristol-Myers Squibb
BMT	Bone marrow transplant
BP	Blast phase
CARES	Corporate Adverse Event Reporting and Evaluation System
CBC	Complete blood count
cCCyR	Confirmed complete cytogenetic response
CCDS	Company Core Data Sheet
CCyR	Complete cytogenetic response
CHF	Congestive heart failure
CHR	Complete haematologic response
CI	Confidence interval
Cmax	Maximum concentration
Cminss	Steady-state trough concentration
CML	Chronic myeloid leukaemia
CMR	Complete molecular response
CNS	Central nervous system
COG	Children Oncology Group
CP	Chronic phase
CSO	Chief Scientific Officer
CSR	Clinical study report
CTC	Common toxicity criteria
CYP	Cytochrome P450 enzyme
DASISION	Dasatinib versus imatinib study in treatment-naïve CML patients
DDR	Discoidin domain receptor

Term	Definition
DLT	Dose-limiting toxicity
DSUR	Developmental Safety Update Report
ECG	Electrocardiogram
EFS	Event-free survival
EPAR	European Public Assessment Report
EPH	Ephrin
ET	Endothelin
EU	European Union
EU-RMP	European Union Risk Management Plan
FDA	The United States Food and Drug Administration
GD	Gestational day
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumour
GPRD	General Practice Research Database
GPV&E	Global Pharmacovigilance and Epidemiology
GVHD	Graft-versus-host disease
HA	Health authority
HCT	Haematopoietic cell transplant
hERG	Human ether-a-go-go-related gene
h	Hour
HLGT	High-level group term
HLT	High-level term
hPAEC	Human pulmonary artery endothelial cells
hPASM	Human pulmonary artery smooth muscle cells
HSCT	Haematopoietic stem cell transplant
IB	Investigator's brochure
ICH	Intracranial haemorrhage
IFN	Interferon
IS	International Standard
IST	Investigator-sponsored trial
kg	Kilogram
LD	Lactation day
LVEF	Left ventricular ejection fraction
m^2	Square meter
MAH	Marketing Authorization Holder

Term	Definition
MCyR	Major cytogenetic response
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHR	Major haematologic response
MI	Myocardial infarction
µL	Microlitre
µM	Micromolar
mL	Millilitre
mm^3	Cubic millimeter
MMR	Major molecular response
MR	Molecular response
MRD	Minimal residual disease
msec	Millisecond
MST	Medical Surveillance Team
NA	Not applicable
NEC	Necrotising enterocolitis
ng	Nanogram
NHL	Non-Hodgkin's lymphoma
NO	Nitric oxide
OHR	Overall haematologic response
OS	Overall survival
PA	Pulmonary artery
PAH	Pulmonary artery hypertension
PAOD	Peripheral artery occlusive disease
PAP	Pulmonary arterial pressure
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamic, pharmacodynamics
PDGFR	Platelet-derived growth factor receptor
PFOS	Powder for oral suspension
PFS	Progression-free survival
Ph-	Philadelphia chromosome-negative
Ph+	Philadelphia chromosome-positive
PhV	Pharmacovigilance
PK	Pharmacokinetic, pharmacokinetics
PO	Per os, oral

Term	Definition
PSUR	Periodic Safety Update Report
PT	Preferred term
QD	Once daily
QTc	Corrected QT
QTcF	QTc using Fridericia's method
RHC	Right heart catheterization
SAE	Serious adverse event
SMO	Smoothened transmembrane protein
SmPC	Summary of Product Characteristics
SOC	System Organ Class
START	**S**RC/ABL **T**yrosine kinase inhibition **A**ctivity: **R**esearch **T**rial
TDD	Total daily dose
TKI	Tyrosine kinase inhibitor
UK	United Kingdom
USPI	The United States Package Insert

APPENDIX 1: REFERENCES

16 page(s) excluding cover page

8 APPENDIX 1: REFERENCES

1 Fitzmaurice C. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015. A systematic analysis for the global burden of disease study. JAMA Oncol. 2017;3(4):524-548.

2 American Cancer Society. Cancer Facts & Figures 2017. Atlanta: American Cancer Society; 2017.

3 Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014 Jan-Feb;64(1):9-29.

4 Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2012 update on diagnosis, monitoring, and management. Am J Hematol. 2012 Nov;87(11):1037-45.

5 Rohrbacher M, Hasford J. Epidemiology of chronic myeloid leukaemia (CML). Best Pract Res Clin Haematol. 2009 Sep;22(3):295-302.

6 Bhayat F, Das-Gupta E, Smith C, McKeever T, Hubbard R. The incidence of and mortality from leukaemias in the UK: a general population-based study. BMC Cancer. 2009 Jul 26;9:252.

7 Smith MA, Ries LAG, Gurney JG, Ross JA. Leukemia in Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds). Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995, National Cancer Institute, SEER Program. NIH Pub. No. 99-4649. Bethesda, MD, 1999.

8 Huang X, Cortes J, Kantarjian H. Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. Cancer. 2012 Jun 15;118(12):3123-7.

9 Lithuania Cancer Registry. Prevalence. 5/27/2016]; Available from: http://www.nvi.lt/index.php?-1473131582

10 Engholm G, Ferlay J, Christensen N, Kejs AMT, Johannesen TB, Khan S, Leinonen MK, Milter MC, Ólafsdóttir E, Petersen T, Trykker H, Storm HH. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 7.2 (16.12.2015). Association of the Nordic Cancer Registries. Danish Cancer Society. Available from http://www.ancr.nu, accessed on 06 June 2016.

11 AIRTUM. I tumori in Italia • Rapporto AIRTUM 2015. Rare Haematological Diseases. Prevalence. Epidemiol Prev 40 (1) Suppl 2:1-120.

[12] Gunnarsson, N., et al., Population-based assessment of chronic myeloid leukemia in Sweden: striking increase in survival and prevalence. Eur J Haematol. 2016 Feb 2.

[13] Alvarez RH, Cortes JE. The Biology of Chronic Myelogenous Leukemia: Implications for Imatinib Therapy. Seminars in Hematology, 2007. 44 (suppl 1): p. S4-S14.

[14] Ries LAG, Melbert D, Krapcho M, Stinchcomb DG, Howlader N, Horner MJ, Mariotto A, Miller BA, Feuer EJ, Altekruse SF, Lewis DR, Clegg L, Eisner MP, Reichman M, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2005, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2005/, based on November 2007 SEER data submission, posted to the SEER web site, 2008.

[15] United Kingdom Leukaemia Research Fund website: http://www.lrf.org.uk/en/1/disstahome.html accessed on March 05, 2008.

[16] Hahn EA, Sorensen MV, Hudgens SA, et al. Quality of life in patients with newly diagnosed chronic phase chronic myeloid leukemia on imatinib versus interferon alfa plus low-dose cytarabine: results from the IRIS Study. Journal of Clinical Oncology, 2003. 21(11): p. 2138-46.

[17] Faderl S, T.M., Estrov Z, O'Brien S, Kurzrock R, Kantarjian HM, The biology of chronic myeloid leukemia. New England Journal of Medicine, 1999. 341(3): p. 164-72.

[18] Mendizabal AM, Garcia-Gonzalez P, Levine PH. Regional variations in age at diagnosis and overall survival among patients with chronic myeloid leukemia from low and middle income countries. Cancer Epidemiol. 2013 Jun;37(3):247-54.

[19] Aoki, EA. Correlation of Different Responses to Imatinib on Survival of Patients (pts) with Chronic Myelogenous Leukemia (CML) in Accelerated (AP) and Blast Phase (BP) [abstract]. Blood, 2005. 106(11): p. 1103.

[20] Matasar MJ, Consedine N, Magai C, et al. Incidence rates of the major leukemia subtypes among U.S. Hispanics, Blacks, and non-Hispanic Whites. Leukemia & Lymphoma, 2006. 47(11): p. 2365-70.

[21] D'Antonio J. Chronic myelogenous leukemia. Clin J Oncol Nurs. 2005 Oct;9(5):535-8.

[22] Vlaanderen J, Lan Q, Kromhout H, Rothman N, Vermeulen R. Occupational benzene exposure and the risk of chronic myeloid leukemia: a meta-analysis of cohort studies incorporating study quality dimensions. Am J Ind Med. 2012 Sep;55(9):779-85.

[23] Kabat GC, Wu JW, Moore SC, Morton LM, Park Y, Hollenbeck AR, Rohan TE. Lifestyle and Dietary Factors in Relation to Risk of Chronic Myeloid Leukemia in the NIH-AARP Diet and Health Study. Cancer Epidemiol Biomarkers Prev. 2013 May;22(5):848-54.

[24] Strom SS, Yamamura Y, Kantarijian HM, Cortes-Franco JE. Obesity, weight gain, and risk of chronic myeloid leukemia. Cancer Epidemiol Biomarkers Prev. 2009 May;18(5):1501-6.

[25] Cnattingius S, Zack M, Ekbom A, gunnarskog J, Linet M, Adami H. Prenatal and Neonatal Risk Factors for Childhood Myeloid Leukemia. Cancer Epidemiology, Biomarkers and Prevention, 1995. 4(5):441-445.

[26] Chihara D, Ito H, Matsuda T, Katanoda K, Shibata A, Saika K, Sobue T, Matsuo K. Decreasing trend in mortality of chronic myelogenous leukemia patients after introduction of imatinib in Japan and the U.S. Oncologist. 2012;17(12):1547-50.

[27] Kantarjian H, O'Brien S, Jabbour E, Garcia-Manero G, Quintas-Cardama A, San J, Rios MB, Ravandi F, Faderl S, Kadia T, Borthakur G, Huang X, Champlin R, Talpaz M, Cortes J. Improved survival in chronic myeloid leukemia since the introduction of imatinib therapy: a single-institution historical experience. Blood 2012 Mar 1;119(9):1981-7.

[28] Husereau D. Imatinib mesylate for chronic myeloid leukemia: what do we really know? Issues in Emering Health Technology, 2002. 42: p. 1-4.

[29] National Cancer Institute. Cancer Stat Facts: Leukemia - Chronic Myeloid Leukemia. https://seer.cancer.gov/statfacts/html/cmyl.html. Accessed on 2 February 2018.

[30] Cortes J, Quiinta A, Giles F, et al. Erythropoietin Is Effective in Improving the Anemia Induced by Imatinib Mesylate Therapy in Patients with Chronic Myeloid Leukemia in Chronic Phase. Cancer, 2004. 100(11): p. 2396-402.

[31] Breccia M, Stefanizzi C, Cannella L et al. Differences in hematological and non-hematological toxicity during treatment with imatinib in patients with early and late phase chronic myeloid leukemia. Leuk & Lymphoma 2008; 49:2328-32.

[32] Sneed TB, Kantarjian HM, Talpaz M et al. The Significance of Myelosuppression during Therapy with Imatinib Mesylate in Patients with Chronic Myeloid Leukemia in Chronic Phase. Cancer 2004;100:116-21.

[33] Cortes JE, Baccarani M, Guilhot F et al. Phase III, Randomized, Open-Label Study of Daily Imatinib Mesylate 400mg Versus 800mg in Patients with Newly Diagnosed, Previously Untreated Chronic Myeloid Leukemia in Chronic Phase Using Molecular End Points: Tyrosine Kinase Inhibitor Optimization and Selectivity Study. JCO 2010; 28:424-30.

[34] Wolf D and Rumpold H. A Benefit-Risk Assessment of Imatinib in Chronic Myeloid Leukaemia and Gastrointestinal Stromal Tumours. Drug Saf 2003;32:1001-15.

[35] Bouwmans C, Janssen J, Huijgens P et al. Costs of haematological adverse events in chronic myeloid leukaemia patients: a retrospective cost analysis of the treatment of anemia, neutropenia and thrombocytopenia in patients with chronic myeloid leukaemia. J Med Econ 2009;12:164-9.

[36] Cortes JE, Kantarjian HM, Goldberg SL et al. High-dose Imatinib in Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia: High Rates of Rapid Cytogenetic and Molecular Responses. JCO 2009;27:4754-59.

[37] Kantarjian H, Talpaz M, O'Brien S et al. High-dose imatinib mesylate therapy in newly diagnosed Philadelphia chromosome-positive chronic phase chronic myeloid leukemia. Blood 2004;103:2873-78.

[38] Cortes JE, Jones D, O'Brien S et al. Nilotinib As Front-Line Treatment for Patients With Chronic Myeloid Leukemia in Early Chronic Phase. JCO 2010;28:392-97.

[39] Deininger MWN, Ford JM, Druker BJ. Practical Management of Patients with Chronic Myeloid Leukemia Receiving Imatinib. Journal of Clinical Oncology, 2003. 21(8): p. 1637-47.

[40] Kantarjian H, Wunderle L, Bhalla K, et al. Nilotinib in Imatinib-Resistant CML and Philadelphia Chromosome-Positive ALL. New Eng J Med. 2006; 354(24):2542-51.

41 Millot F, Guilhot J, Nelken B et al. Imatinib mesylate is effective in children with chronic myelogenous leukemia in late chronic and advanced phase and in relapse after stem cell transplantation. Leukemia 2006; 20:187-92.

42 Wehmeier A, Daum I, Jamin H, Schneider W. Incidence and clinical risk factors for bleeding and thrombotic complications in myeloproliferative disorders. A retrospective analysis of 260 patients. Ann Hematol. 1991 Aug;63 (2):101-6.

43 Ebnöether M, Stentoft J, Ford J, et al. Cerebral oedema as a possible complication of treatment with imatinib. Lancet 2002; 359:1751-2.

44 Song KW, Al-Beirouti B, Yee K, et al. Subdural Hematomas during CML Therapy with Imatinib Mesylate. Leukemia & Lymphoma, 2004; 45(8): p. 1633-36.

45 Soylu AR, B.Y., Cetiner D, Buyukasid NS, Koca E, Haznedaroglu IC, Ozcebe OI, Simsek H,Overt gastrointesinal bleeding in haematoloic neoplasms. Digestive and Liver Disease, 2005.

46 Kessler CM, K.H., Havlik RJ, Uncontolled thrombocytosis in chronic myeloproliferative disorders. British Journal of Haematology. 1982; 50:157-167.

47 Grove CS. Vascular endothelial growth factor: the key mediator in pleural effusion formation. Current Opinion in Pulmonary Medicine, 2002. 8: p. 294-301.

48 Bass J. Thoracentesis in Patients with Hematologic Malignancy: Yield and Safety. CHEST, 2005. 127: p. 2101-5.

49 Unnikrishnan D, Garl S, Varshneya N, et al. Cardiac monitoring of patients receiving arsenic trioxide therapy. British Journal of Haematology, 2004. 124: p. 640-17.

50 Alexandrakis MG, Kyriakou DS, Bouros D. Pleural Effusions in Hematologic Malignancies. CHEST, 2004. 125: p. 1546-55.

51 American Cancer Society. Cancer Facts & Figures 2017. Atlanta: American Cancer Society; 2017.

[52] Josep-Maria Ribera (2011). Acute Lymphoblastic Leukemia in Adolescents and Young Adults, Acute Leukemia The Scientist's Perspective and Challenge, Prof. Mariastefania Antica (Ed.), ISBN: 978-953-307-553-2, InTech, Available from: http://www.intechopen.com/books/acute-leukemia-the-scientist-s-perspective-andchallenge/acute-lymphoblastic-leukemia-in-adolescents-and-young-adults

[53] Juliusson G, Karlsson K, Hallböök H. Population-based analyses in adult acute lymphoblastic leukemia. Blood. 2010 Aug 12;116(6):1011

[54] de Souza Reis R Sr, de Camargo B, de Oliveira Santos M, de Oliveira JM, Azevedo Silva F, Pombo-de-Oliveira MS. Childhood leukemia incidence in Brazil according to different geographical regions. Pediatr Blood Cancer. 2011 Jan;56(1):58-64.

[55] Velangi MR, Reid MM, Bown N, Jackson GH, Summerfield GP, Proctor SJ, Taylor PR. Acute lymphoblastic leukaemia of the L3 subtype in adults in the Northern health region of England 1983-99. J Clin Pathol. 2002 Aug;55(8):591-5.

[56] Lamvik J, Waage A, Wahl SG, Naess I, Paulsen PQ, Hammerstrøm J. Adult acute lymphoblastic leukemia, Burkitt's lymphoma and lymphoblastic lymphoma in middle Norway 1985-2004. Haematologica. 2006 Oct;91(10):1428-9.

[57] AIRTUM. TUMORI IN ITALIA - RAPPORTO 2014 Prevalenza e guarigione da tumore in Italia ITALIAN CANCER FIGURES - REPORT 2014 Prevalence and cure of cancer in Italy. Epidemiol Prev 38 (6) Suppl 1:1-144.

[58] Dores GM, Devesa SS, Curtis RE, Linet MS, Morton LM. Acute leukemia incidenc and patient survival among children and adults in the United States, 2001-2007. Blood. 2012 Jan 5;119(1):34-43.

[59] Vlaanderen J, Lan Q, Kromhout H, Rothman N, Vermeulen R. Occupational benzene exposure and the risk of lymphoma subtypes: a meta-analysis of cohort studies incorporating three study quality dimensions. Environ Health Perspect. 2011 Feb;119(2):159-67.

[60] Apostolidou E, Swords R, Alvarado Y, Giles FJ. Treatment of acute lymphoblastic leukaemia : a new era. Drugs. 2007;67(15):2153-71.

[61] Faderl S, Jeha S, Kantarjian H. The biology and therapy of adult acute lymphoblastic leukemia. Cancer. 2003; 98(7):1337-54.

62 National Cancer Institute. Cancer Stat Facts: Leukemia - Acute Lymphocytic Leukemia. https://seer.cancer.gov/statfacts/html/alyl.html. Accessed on 14 June 2018.

63 Bhayat F, Das-Gupta E, Smith C, McKeever T, Hubbard R. The incidence of and mortality from leukaemias in the UK: a general population-based study. BMC Cancer. 2009 Jul 26;9:252.

64 Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: A comprehensive review and 2017 update. Blood Cancer J. 2017; 7: e577

65 Lilly, M.B., et al., Dasatinib 140 mg once daily versus 70 mg twice daily in patients with Ph-positive acute lymphoblastic leukemia who failed imatinib: Results from a phase 3 study. Am J Hematol, 2010. 85(3): p. 164-70.

66 https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/gleevec_tabs.pdf accessed 27 May 2016

67 Ku, G.H., et al., Venous thromboembolism in patients with acute leukemia: incidence, risk factors, and effect on survival. Blood. 2009 Apr 23;113(17):3911-7.

68 Ziegler, S., et al., Symptomatic venous thromboembolism in acute leukemia. Incidence, risk factors, and impact on prognosis. Thromb Res, 2005. 115(1-2): p. 59-64.

69 De Stefano, V., et al., The risk of thrombosis in patients with acute leukemia: occurrence of thrombosis at diagnosis and duringtreatment. J Thromb Haemost. 2005 Sep;3(9):1985-92.

70 Melillo, L., et al., Symptomatic venous thromboembolism and thrombophilic status in adult acute leukemia: a single-center experience of 114 patients at diagnosis. Acta Haematol, 2007. 117(4): p. 215-20.

71 Mohren, M., et al., Increased risk of venous thromboembolism in patients with acute leukaemia. Br J Cancer, 2006. 94(2): p. 200-2

72 Lauw, M.N., et al., Venous thromboembolism in adults treated for acute lymphoblastic leukaemia: Effect of fresh frozen plasma supplementation. Thromb Haemost, 2013. 109(4): p. 633-42.

73 Vu, K., et al., A retrospective study of venous thromboembolism in acute leukemia patients treated at the University of Texas MD Anderson Cancer Center. Cancer Med, 2015. 4(1): p. 27-35.

[74] Duarte X, Esteves S, Neto A, Pereira F. Incidence and risk factors for CNS thrombosis in paediatric acute lymphoblastic leaukaemia during intenstive asparaginase treatment: a single-centre cohort study. Br J Haematol 2016; 174(2):280-91.

[75] Labar, B., et al., Dexamethasone compared to prednisolone for adults with acute lymphoblastic leukemia or lymphoblastic lymphoma: final results of the ALL-4 randomized, phase III trial of the EORTC Leukemia Group. Haematologica, 2010. 95(9): p. 1489-95.

[76] Lilly, M.B., et al., Dasatinib 140 mg once daily versus 70 mg twice daily in patients with Ph-positive acute lymphoblastic leukemia who failed imatinib: Results from a phase 3 study. Am J Hematol, 2010. 85(3): p. 164-70.

[77] Thomas, X., et al., Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. J Clin Oncol, 2004. 22(20): p. 4075-86.

[78] Nonclinical Pharmacology Written Summary. Bristol-Myers Squibb Company; 2005. Document Control No. 930012177.

[79] BMS-354825: Oral study of fertility and early embryonic development in rats (Study DN07028). Bristol-Myers Squibb Company; 2007. Document Control No. 930026487.

[80] BMS-354825: Oral Study on embryo-fetal development in rats (Study DN04078). Bristol-Myers Squibb Company; 2005. Document Control No. 930011508.

[81] BMS-354825: Oral study on embryo-fetal development in rabbits (Study DN04080). Bristol-Myers Squibb Company; 2005. Document Control No. 930010604.

[82] Dasatinib (BMS-354825): Oral Range-Finding Study of Peri- and Postnatal Development in Rats (Study DN10077). Bristol-Myers Squibb Company; 2011. Document Control Number 930051220.

[83] BMS-354825: Single-dose oral cardiovascular safety pharmacology study in monkeys (Study DS03098). Bristol-Myers Squibb Company; 2003. Document Control No. 930005453.

[84] BMS-354825: Nine-month oral toxicity study in cynomolgus monkeys (Study DS03073). Bristol-Myers Squibb Company; 2005. Document Control No. 930011520.

[85] BMS-354825: Six-month oral toxicity study in rats (Study DS03072). Bristol-Myers Squibb Company; 2005. Document Control No. 930011518.

[86] BMS-354825: Oral carcinogenicity study in rats (Study DS07137). Bristol-Myers Squibb Company; 2007. Document Control No. 930048153.

[87] In vitro and in vivo evaluation of dasatinib and imatinib on physiological parameters of pulmonary arterial hypertension. AACR Annual Meeting 2013 (Poster Presentation); Abstract # 2426

[88] BMS-354825: One-month oral investigative cardiotoxicity study in mice (Study DS07053); Bristol-Myers Squibb Company; 2007. Document Control No. 930023413.

[89] BMS-354825: Neutral red uptake phototoxicity assay in Balb/c 3T3 mouse fibroblasts (Study DS05008). Bristol-Myers Squibb Company; 2005. Document Control No 930012310.

[90] BMS-354825: Single-dose oral phototoxicity study in hairless mice (Study DN07138). Bristol-Myers Squibb Company; 2008. Document Control No. 930026736.

[91] In vitro evaluation of BMS-354825 as an inhibitor of human cytochrome P450 enzymes. Bristol-Myers Squibb Company; 2005. Document Control No. 930011322.

[92] In vitro assessment of BMS-354825 as an inducer of human cytochrome P450 expression in cultured human hepatocytes. Bristol-Myers Squibb Company; 2005. Document Control No. 930011325.

[93] Dasatinib Summary of Product Characteristics. Bristol–Myers Squibb; 19 November 2012.

[94] Dasatinib summary of clinical safety module 2.7.4 2012 DCN 930059231.

[95] Pharmacokinetic study report of CA180002. A phase I dose-escalation study to determine the safety, pharmacokinetics, and pharmacodynamics of BMS-354825 in the treatment of patients with chronic, accelerated, or blast phase chronic myelogenous leukemia, or Philadelphia chromosome positive acute lymphoblastic leukemia who have hematologic resistance to imatinib mesylate (Gleevec□): Pharmacokinetics Study Report. Bristol-Myers Squibb Pharmaceutical Research Institute; 2005. Document Control No. 930012788.

[96] Final clinical study report for Study CA180005: A Phase 2 study of dasatinib (BMS-354825) in subjects with accelerated phase chronic myeloid leukemia resistant to or intolerant of imatinib mesylate. Bristol-Myers Squibb Company; 2008. Document Control No. 930025910.

97 Final clinical study report for Study CA180006: A Phase 2 study of BMS-354825 in subjects with myeloid blast phase chronic myeloid leukemia resistant to or intolerant of imatinib mesylate. Bristol-Myers Squibb Company; 2008. Document Control No. 930025793.

98 Clinical study report for Study CA180013: A Phase 2 study to determine the activity of BMS-354825 in subjects with chronic phase Philadelphia chromosome positive chronic myeloid leukemia who have disease that is resistant to imatinib mesylate (Gleevec®) or who are intolerant of imatinib. Bristol-Myers Squibb Company; 2008. Document Control No. 930026166.

99 Final clinical study report for Study CA180015: Subjects with lymphoid blast phase CML: A Phase 2 study of BMS-354825 in subjects with lymphoid blast phase chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia resistant to or intolerant of imatinib mesylate. Bristol-Myers Squibb Company; 2008. Document Control No. 930025377.

100 Final clinical study report for Study CA180015: Subjects with Philadelphia chromosome-positive acute lymphoblastic leukemia resistant: A Phase 2 study of BMS-354825 in subjects with lymphoid blast phase chronic myeloid leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia resistant to or intolerant of imatinib mesylate. Bristol-Myers Squibb Company; 2008. Document Control No. 930025471.

101 Final clinical study report for Study CA180017: A randomized multicenter open label study of dasatinib vs imatinib mesylate 800 mg/day in subjects with chronic phase Philadelphia chromosome-positive chronic myeloid leukemia who have disease that is resistant to imatinib at a dose of 400 - 600 mg/day. Bristol-Myers Squibb Company; 2007. Document Control No. 930019651.

102 Final clinical study report for Study CA180031: A Phase I/II study of BMS-354825 in subjects with imatinib resistant or intolerant chronic myelogenous leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia who are resistant or intolerant to treatment. Bristol Myers Squibb Company; 2008. Document Control No. 930024785.

[103] Clinical study report for Study CA180034: A randomized two-by-two, multicenter, open-label phase 3 study of BMS 354825 administered orally at a dose of 50 mg or 70 mg twice daily or 100 mg or 140 mg once daily in patients with chronic phase Philadelphia chromosome or BCR-ABL positive chronic myelogenous leukemia who are resistant or intolerant to imatinib mesylate. Bristol-Myers Squibb Company; 2007. Document Control No. 930020746.

[104] Clinical study report addendum for Study CA180034: A randomized two-by-two, multicenter, open-label phase 3 study of BMS 354825 administered orally at a dose of 50 mg or 70 mg twice daily or 100 mg or 140 mg once daily in patients with chronic phase Philadelphia chromosome or BCR-ABL positive chronic myelogenous leukemia who are resistant or intolerant to imatinib mesylate. Bristol-Myers Squibb Company; 2011. Document Control No. 930053938.

[105] Addendum 02 to final clinical study report for Study CA180034: A randomized two-by-two, multicenter, open-label phase 3 study of BMS 354825 administered orally at a dose of 50 mg or 70 mg twice daily or 100 mg or 140 mg once daily in patients with chronic phase Philadelphia chromosome or BCR-ABL positive chronic myelogenous leukemia who are resistant or intolerant to imatinib mesylate. Seven year Clinical Study Report. Bristol-Myers Squibb Company; 2014. Document Control No. 930079661.

[106] A randomized two-by-two, multicenter, open-label Phase 3 study of BMS-354825 administered orally at a dose of 50 mg or 70 mg twice daily or 100 mg or 140 mg once daily in patients with chronic phase Philadelphia chromosome or BCR-ABL positive chronic myelogenous leukemia who are resistant or intolerant to imatinib mesylate. Final Study Report (CA180034). Bristol-Myers Squibb Pharmaceutical Research Institute; July 2008. Document Control No. 930029367.

[107] A randomized, two-arm, multicenter, open-label Phase III study of BMS-354825 administered orally at a dose of 70 mg twice daily or 140 mg once daily in subjects with chronic myeloid leukemia in accelerated phase or in myeloid or lymphoid blast phase or with Philadelphia chromosome positive acute lymphoblastic leukemia who are resistant or intolerant to imatinib mesylate. CA180035. Final Study Report. Bristol-Myers Squibb Pharmaceutical Research Institute; July 2008. Document Control No. 930029431

[108] Addendum 01 to final CSR for Study CA180035: A randomized, two-arm, multicenter, open-label phase III study of BMS 354825 administered orally at a dose of 70 mg twice daily or 140 mg once daily in subjects with chronic myeloid leukemia in accelerated phase or in myeloid or lymphoid blast phase or with Philadelphia chromosome positive acute lymphoblastic leukemia who are resistant or intolerant to imatinib mesylate. Bristol-Myers Squibb Company; 2012. Document Control No. 930056163.

[109] Interim clinical study report for Study CA180035: A randomized, two-arm, multicenter, open-label Phase III study of BMS-354825 administered orally at a dose of 70 mg twice daily or 140 mg once daily in subjects with chronic myeloid leukemia in accelerated phase or in myeloid or lymphoid blast phase or with Philadelphia chromosome positive acute lymphoblastic leukemia who are resistant or intolerant to imatinib mesylate. Bristol-Myers Squibb Company; 2007. Document Control No. 930020749.

[110] Clinical study report for Study CA180036: A study to document the long-term safety and efficacy of BMS 354825 in subjects with imatinib resistant or intolerant chronic myelogenous leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia who are resistant or intolerant to previous treatment and have completed the previous Phase I/II Protocol (CA180 031). Bristol-Myers Squibb Company; 2010. Document Control No. 930043958.

[111] Clinical study report for Study CA180039: Synoptic report: Long-Term Safety and Efficacy of Dasatinib in Chronic Myelogenous Leukemia or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia in Subjects who Experienced Clinical Benefit on Protocol CA180002. Bristol Myers Squibb Company; 2008. Document Control No. 930033042.

[112] Final clinical study report for Study CA180043: Synoptic report: An Open-Label Randomized Study of Dasatinib vs. High-Dose (800 mg) Imatinib in the Treatment of Subjects with Chronic Phase Chronic Myeloid Leukemia Who Have Had a Suboptimal Response After at Least 3 Months of Therapy with 400 mg Imatinib. Bristol Myers Squibb Company; 2010. Document Control No. 930048395.

[113] 24-Month follow-up report for Study CA180056: An open-label, randomized, multicenter Phase III trial of dasatinib (SPRYCEL®) vs standard dose imatinib (400 mg) in the treatment of subjects with newly diagnosed chronic phase Philadelphia chromosome positive chronic myeloid leukemia. Bristol-Myers Squibb Company; 2011. Document Control No. 930051136.

[114] 36-Month follow-up report for Study CA180056: An open-label, randomized, multicenter Phase III trial of dasatinib (SPRYCEL®) vs standard dose imatinib (400 mg) in the treatment of subjects with newly diagnosed chronic phase Philadelphia chromosome positive chronic myeloid leukemia. Bristol-Myers Squibb Company; 2012. Document Control No. 930058629.

[115] 48-Month follow-up report for Study CA180056: An open-label, randomized, multicenter Phase III trial of dasatinib (SPRYCEL®) vs standard dose imatinib (400 mg) in the treatment of subjects with newly diagnosed chronic phase Philadelphia chromosome positive chronic myeloid leukemia. Bristol-Myers Squibb Company; 2013. Document Control No. 930069171.

[116] 5-year follow-up report for Study CA180056: An open-label, randomized, multicenter Phase III trial of dasatinib (SPRYCEL®) vs standard dose imatinib (400 mg) in the treatment of subjects with newly diagnosed chronic phase Philadelphia chromosome positive chronic myeloid leukemia. Bristol-Myers Squibb Company; 2014. Document Control No. 930080218.

[117] Clinical study report for Study CA180138: A randomized, multicenter, open-label non-comparative Phase II study of BMS 354825 administered orally at a dose of 50 mg twice daily or 100 mg once daily in subjects with chronic phase Philadelphia chromosome positive chronic myeloid leukemia (CML) who are resistant or intolerant to imatinib. Bristol Myers Squibb Company; 2010. Document Control No. 930043957.

[118] Study CA180160 efficacy and safety update: A Phase 2 study to determine the activity of dasatinib administered orally (PO) at a dose of 100 mg QD in chronic phase chronic myelogenous leukemia (CML), at a dose of 70 mg BID in advanced phase chronic myelogenous leukemia (CML) Chinese subjects who are resistant to or intolerant of imatinib mesylate (Gleevec®). Bristol-Myers Squibb Company; 2009. Document Control No. 930046813.

[119] Final clinical study report for Study CA180188: Synoptic report: Dasatinib in chronic myelogenous leukemia or Philadelphia chromosome positive acute lymphoblastic leukemic subjects who are experiencing clinical benefit on current START or CA180039 protocols: Long term safety and efficacy analysis. Bristol-Myers Squibb Company; 2012. Document Control No. 930056599.

[120] Final clinical study report for Study CA180018: Phase 1 study of SRC/ABL tyrosine kinase inhibitor dasatinib (BMS 354825) in children and adolescents with relapsed or refractory leukemia, Protocol ITCC 005. Bristol-Myers Squibb Company; 2011. Document Control No. 930054958.

[121] Zwaan CM, Rizzari C, Mechinaud F, et al. Dasatinib in children with relapsed or refractory leukemia: results of the CA180-018 Phase I dose-escalation study of the Innovative Therapies for Children with Cancer consortium. J Clin Oncol 2013 May 28 [Epub ahead of print].

[122] Clinical study report for Study CA180038: A Phase 1 study of BMS-354825 (Dasatinib) in children with recurrent/refractory solid tumors or imatinib resistant Ph+ leukemia (Children's Oncology Group ADVL0516). Bristol-Myers Squibb Company; 2009. Document Control No. 930039548.

[123] Aplenc R, Blaney SM, Strauss LC, et al. Pediatric Phase I trial and pharmacokinetic study of dasatinib: a report from the Children's Oncology Group Phase I Consortium. J Clin Oncol 2011; 29(7):839-44.

[124] Dasatinib Clinical Study Report for Study CA180204 Intensified Tyrosine Kinase Inhibitor Therapy (Dasatinib: IND# 73969, NSC# 732517) in Philadelphia Positive Acute Lymphoblastic Leukemia (ALL). Bristol Myers Squibb Company; 2015. Document Control Number 930092723.

[125] Interim analysis for Study CA180226: A Phase 2 study of dasatinib therapy in children and adolescents with newly diagnosed chronic phase myelogenous leukemia or with Ph+ leukemias resistant or intolerant to imatinib. Bristol-Myers Squibb Company; 2012. Document Control No. 930065503.

[126] Single dose pharmacokinetics of dasatinib in patients with hepatic impairment compared to healthy adult patients (Study CA180051). Clinical Study Report. Bristol-Myers Squibb Company; 2008. Document Control No. 930026108.

[127] Randomized, Multicenter Phase III Trial of Dasatinib (SPRYCEL®) vs Standard Dose Imatinib (400 mg) in the Treatment of Subjects with Newly Diagnosed Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia 5-Year Follow-Up. Bristol-Myers Squibb; 2014. Document Control No. 930080218.

[128] Clinical Study Report CA180005 A Phase 2 Study of Dasatinib (BMS-354825) in Subjects with Accelerated Phase Chronic Myeloid Leukemia Resistant to or Intolerant of Imatinib Mesylate. Bristol-Myers Squibb; 2008. Document Control No. 930013152.

[129] Clinical Study Report: CA180056 An Open-Label, Randomized, Multicenter Phase III Trial of Dasatinib (SPRYCEL) vs Standard Dose Imatinib (400 mg) in the Treatment of Subjects with Newly Diagnosed Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia 5-Year Follow-Up. Bristol-Myers Squibb Company. 2014. Document Control No. 930080218.

[130] Dasatinib (BMS-354825) MODULE 2.5: CLINICAL OVERVIEW Indication: Treatment of Pediatric Ph+ Acute Lymphoblastic Leukemia (Ph+ ALL). Bristol-Myers Squibb Company; 2017. Document Control No 930120128.

[131] Surveillance Research Program, National Cancer Institute SEER*Stat software (www.seer.cancer.gov/seerstat) version 8.3.2.

[132] Dasatinib summary of clinical safety module 2.7.4 2017 DCN 930111243

[133] Pietras K, Östman A, Sjöquist M, et al. Inhibition of platelet-derived growth factor receptors reduces interstitial hypertension and increases transcapillary transport in tumors. Cancer Res 2001; 61:2929-34.

[134] Mustjoki S, Auvinen K, Kreutzman A, et al. Leukemia. 2013 Apr;27(4):914-24.

[135] Quintas-Cardama A, Kantarjian H, Ravandi F, et. al. Bleeding diathesis in patients with chronic myelogenous leukemia receiving dasatinib therapy. Cancer. 2009 Mar 11.

[136] Gratacap, M-P, Martin, V, Valera, M-C, et al. The new tyrosine-kinase inhibitor and anti-cancer drug dasatinib reversibly affects platlet activation in vitro and in vivo. Blood. 2009; 114:1884–92

[137] Unnikrishnan D, Garl S, Varshneya N, et al. Cardiac monitoring of patients receiving arsenic trioxide therapy. British Journal of Haematology, 2004. 124: p. 640-17.

[138] Dasatinib Pulmonary Arterial Hypertension Update Report; 930070640;30-May-2013

[139] George, JN, Nester, CM. Syndromes of Thrombotic Microangiopathy. N Engl J Med 2014;371:654-66.

[140] Martino S, Daguindau E, Ferrand C, Bamoulid J, Hayette, S, Nicolini FE, Capellier G, Ceconinck E, Larosa F. A successful renal transplantation for renal failure after dasatinib-induced thrombotic thrombocytopenic purpura in a patient with imatinib-resistant chronic myelogenous leukaemia on nilotinib. Leuk Res Rep. 2013 Mar 19;2(1):29-31.

[141] Mittal K, Koon H, Elson P, Triozzi P, Dowlati A, Chen, H, Borden EC Rini BI. Dual VEGF/VEGFR inhibition in advanced solid malignancies. Cancer Biology and Therapy 15:8, 975-981.

[142] Rosamond W, Flegal K, Friday G, et al. American Heart Association, Heart Disease and Stroke Statistics-2007 Update, A.H. Association, Editor. 2007, American Heart Association: Dallas, Texas.

[143] Hobernicht, S.et al. BRIEF REPORT Acquired Growth Hormone Deficiency in a Girl With Chronic Myelogenous Leukemia Treated With Tyrosine Kinase Inhibitor Therapy Pediatr Blood Cancer 2011;56:671–673.

[144] Harr, T. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Orphanet Journal of Rare Diseases 2010, 5:39

[145] French, LE. Toxic Epidermal Necrolysis and Stevens Johnson Syndrome: Our Current Understanding Allergology International. 2006; 55: 9-16

[146] Lamoreux MR, Sternbach MR, Hsu WT. Erythema multiforme. Am Fam Physician. 2006 Dec 1;74(11):1883-8

[147] Struck MF, Hilbert P, Mockenhaupt M, Reichelt B, Steen M. Severe cutaneous adverse reactions: emergency approach to non-burn epidermolytic syndromes. Intensive Care Med. Jan 2010;36(1):22-32.

[148] Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, et al. Medical genetics: a marker for Stevens-Johnson syndrome. Nature. Apr 1 2004;428(6982):486.

[149] Ferrell PB Jr, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics. Oct 2008;9(10):1543-6

[150] Gerull R1, Nelle M, Schaible T. Crit Care Med. 2011 Jun;39(6):1521-32. doi: 10.1097/CCM.0b013e31821201ed.

[151] P450 Drug Interaction Table. Available at http://medicine.iupui.edu/clinpharm/ddis/table.aspx. Accessed 15-Jul-2014

[152] http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm.

APPENDIX 2: NONCLINICAL SAFETY SUMMARY

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APPENDIX 2: NONCLINICAL SAFETY SUMMARY

The nonclinical safety profile of dasatinib was well characterized in a drug-safety program including a battery of in vitro and in vivo studies in rats, rabbits, monkeys, and dogs.

In single- and repeat-dose studies in rats and monkeys, dasatinib primarily affected the rapidly dividing cells of the GI, lymphoid-organ, and haematopoietic (bone marrow) systems and, to a lesser degree, the kidney. Reversible GI toxicity was the dose-limiting toxicity (DLT) in repeat-dose studies in both animal species, but was manageable by temporary cessation of dosing or dose reduction. Bone-marrow toxicity was a consistent finding in rats following single or repeat doses, and was accompanied by decreases in erythrocyte, lymphocyte, and platelet counts. In monkeys, minimal bone marrow toxicity was limited to a small number of animals following repeat dosing, and was generally accompanied by a decrease in erythrocyte and lymphocyte counts. Bone-marrow toxicity in animals was reversible following cessation of drug treatment. In single-dose studies in rats and monkeys, renal epithelial cell vacuolation and/or tubular dilatation were observed at doses associated with severe toxicity or mortality, whereas renal toxicity in repeat-dose studies was limited to an increase in background kidney mineralization in the 9-month monkey study. Cutaneous haemorrhage was observed following single oral doses in monkeys that resulted in clinical exposure margins of 6x, but did not occur at lower systemic exposures in repeat-dose studies in monkeys or in rats.

Dasatinib was not mutagenic in bacterial mutation assays (Ames test). Dasatinib was clastogenic in the in vitro Chinese hamster ovary cell assay, but was not clastogenic in the oral micronucleus study in rats at clinical exposure margins up to 7x. In a 2-year carcinogenicity study in rats, the highest dose resulted in a plasma drug exposure generally equivalent to or slightly lower than the human exposure at the range of recommended therapeutic doses. The only noteworthy findings in this study included a statistically significant increase in the combined incidence of squamous cell carcinomas and papillomas in the uterus and cervix in the high-dose females, and a statistically significant increased incidence in prostate adenoma in the low-dose males (when the intermediate and high-doses were excluded from the analysis).

In reproductive toxicology studies, dasatinib resulted in early embryonic death in rats and fetal toxicity in rats and rabbits when dosed from implantation through the completion of organogenesis at doses that did not produce maternal toxicity. In an exploratory reproductive peri- and post-natal study in rats, indirect exposure of pups to dasatinib (in utero or through lactation) caused extensive mortality at sub-therapeutic maternal exposures.

The immunosuppressive potential of dasatinib was documented in the mouse mixed lymphocyte response assay and cardiac transplant studies in mice, and could be effectively managed by dose reduction or changes in dosing schedule.

In conclusion, the battery of nonclinical toxicity studies with dasatinib identified the principal target-organs, genetic, developmental, and immunosuppressive toxicities of dasatinib. The single- and repeat-dose oral toxicity studies with dasatinib adequately predicted the clinical haematologic toxicities that have been subsequently observed in clinical trials. GI toxicity, the DLT in rats and

monkeys, has not been dose limiting in humans at exposures that are equivalent to or higher than exposures associated with GI toxicity in animals, demonstrating that humans are less sensitive to dasatinib-induced GI toxicity. Some of the other effects are expected and are consistent with the toxicity induced by the currently marketed BCR-ABL kinase inhibitors. Overall, based on the intended use of dasatinib in patients with CML or Ph+ ALL, the scope and results of nonclinical pharmacology, pharmacokinetic (PK), and drug safety evaluation programs support the long-term oral administration of dasatinib in this patient population.[1]

REFERENCES

1 Dasatinib Nonclinical Overview. Bristol Myers Squibb Company; 2005. Document Control No. 930013043.

APPENDIX 3: CLINICAL TRIAL EXPOSURE

26 page(s) excluding cover page

APPENDIX 3: CLINICAL TRIAL EXPOSURE

DASATINIB

Clinical trial exposure analyses include cumulative dose and clinical exposure by duration, age, gender, and racial origin. For dasatinib, clinical trial exposure analyses are presented in the following tables:

- **Table 1:** Duration of Dasatinib Exposure in Adult Patients with Newly Diagnosed Ph+ CP CML - Pooled Studies CA180056 and CA180363
- **Table 2:** Duration of Dasatinib Exposure in Adult Ph+ CML Patients with Resistance or Intolerance to Prior Therapy - Pooled Studies CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180160, and CA180188
- **Table 3:** Duration of Dasatinib Exposure in Adult Ph+ ALL Patients with Resistance or Intolerance to Prior Therapy - Pooled Studies CA180002, CA180015, CA180035, CA180160 and CA180188
- **Table 4:** Duration of Dasatinib Exposure Totals in Adult Patients - Pooled Studies CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180056, CA180160, CA180188, and CA180363
- **Table 5:** Duration of Dasatinib Exposure Dose in Adult Patients with Newly Diagnosed Ph+ CP CML - Pooled Stuides CA180056 and CA180363
- **Table 6:** Duration of Dasatinib Exposure Dose in Adult Ph+ CML Patients with Resistance or Intolerance to Prior Therapy - Pooled Studies CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180160, and CA180188
- **Table 7:** Duration of Dasatinib Exposure Dose in Adult Ph+ ALL Patients with Resistance or Intolerance to Prior Therapy - Pooled Studies CA180002, CA180015, CA180035, CA180160 and CA180188
- **Table 8:** Duration of Dasatinib Exposure Dose in Adult Patients - Pooled Studies CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180056, CA180160, CA180188, and CA180363
- **Table 9:** Dasatinib Exposure by Age Group And Gender in Adult Patients with Newly Diagnosed Ph+ CP CML - Pooled Studies CA180056 and CA180363
- **Table 10:** Dasatinib Exposure by Age Group And Gender in Adult Ph+ CML Patients with Resistance or Pooled Studies CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180160, and CA180188

- **Table 11:** Dasatinib Exposure by Age Group And Gender in Adult Ph+ ALL Patients with Resistance or Intolerance to Prior Therapy - Pooled Studies CA180002, CA180015, CA180035, CA180160 and CA180188
- **Table 12:** Exposure by Age Group And Gender in Adult Patients - Pooled Studies CA180002, CA180005, CA180006, CA180013, CA180015,CA180017, CA180034, CA180035, CA180039, CA180056, CA180160, CA180188, and CA180363)
- **Table 13**: Dasatinib Exposure by Ethnic or Racial Origin in Adult Patients with Newly Diagnosed Ph+ CP CML - Pooled Studies CA180056 and CA180363
- **Table 14:** Dasatinib Exposure by Ethnic or Racial Origin in Adult Ph+ CML Patients with Resistance or Intolerance to Prior Therapy - Pooled Studies CA180002, CA180005, CA180006, CA180013, CA180015,CA180017, CA180034, CA180035, CA180039, CA180160, and CA180188
- **Table 15:** Dasatinib Exposure by Ethnic or Racial Origin in Adult Ph+ ALL Patients with Resistance or Intolerance to Prior Therapy - Pooled Studies CA180002, CA180015, CA180035, CA180160 and CA180188
- **Table 16:** Dasatinib Exposure by Ethnic or Racial Origin in Adult Patients - Pooled Studies CA180002, CA180005, CA180006, CA180013, CA180015,CA180017, CA180034, CA180035, CA180039, CA180056, CA180160, CA180188, and CA180363
- **Table 17:** Duration of Dasatinib Exposure in Pediatric Patients, Dasatinib Mono-therapy - Pooled Studies CA180018 and CA180226
- **Table 18:** Duration of Dasatinib Exposure in Pediatric Patients, Dasatinib added to Chemo-therapy - CA180372
- **Table 19:** Duration of Dasatinib Exposure in Pediatric Patients, Dasatinib Mono-therapy - Pooled Studies CA180018 and CA180226
- **Table 20:** Duration of Dasatinib Exposure in Pediatric Patients, Dasatinib added to Chemo-therapy - CA180372
- **Table 21:** Dasatinib Exposure by Age Group And Gender in Pediatric Patients, Dasatinib Mono-therapy - Pooled Studies CA180018 and CA180226
- **Table 22:** Dasatinib Exposure by Age Group And Gender in Pediatric Patients, Dasatinib added to Chemo-therapy - CA180372
- **Table 23:** Dasatinib Exposure by Ethnic or Racial Origin in Pediatric Patients, Dasatinib Mono-therapy - Pooled Studies CA180018 and CA180226
- **Table 24:** Dasatinib Exposure by Ethnic or Racial Origin in Pediatric Patients, Dasatinib added to Chemo-therapy - CA180372

Table 1: Duration of Dasatinib Exposure in Adult Patients with Newly Diagnosed Ph+ CP CML - Pooled Studies CA180056 and CA180363

Duration of exposure	Persons N=324 (%)	Person Time (months)
0 - 3 months	10 (3)	14
3 - 6 months	17 (5)	86
6 - 9 months	10 (3)	73
9 - 12 months	15 (5)	164
12 - 18 months	15 (5)	221
18 - 24 months	9 (3)	183
24 - 30 months	20 (6)	535
30 - 36 months	21 (6)	703
36 - 48 months	33 (10)	1434
48 - 60 months	22 (7)	1247
60 - 72 months	143 (44)	9229
72 - 84 months	7 (2)	530
84 - 96 months	2 (1)	183

Note: This table is based on exposure information from the following studies: CA180056 and CA180363.
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Table 2: Duration of Dasatinib Exposure in Adult Ph+ CML Patients with Resistance or Intolerance to Prior Therapy - Pooled Studies CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180160, and CA180188

Duration of exposure	Persons N=2252 (%)	Person Time (months)
0 - 3 months	374 (17)	523
3 - 6 months	239 (11)	1039
6 - 9 months	179 (8)	1334
9 - 12 months	137 (6)	1423
12 - 18 months	194 (9)	2926
18 - 24 months	155 (7)	3281
24 - 30 months	210 (9)	5571
30 - 36 months	98 (4)	3225
36 - 48 months	129 (6)	5395
48 - 60 months	99 (4)	5398
60 - 72 months	115 (5)	7518
72 - 84 months	112 (5)	8842
84 - 96 months	161 (7)	13994
96 - 108 months	20 (<1)	2093
108 - 120 months	26 (1)	2865
120 - 132 months	4 (<1)	510

Note: This table is based on exposure information from the following studies: CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180160, and CA180188. The underlying study population consists of subjects with Chronic, Accelerated or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
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Table 3: Duration of Dasatinib Exposure in Adult Ph+ ALL Patients with Resistance or Intolerance to Prior Therapy - Pooled Studies CA180002, CA180015, CA180035, CA180160 and CA180188

Duration of exposure	Persons N=136(%)	Person Time (months)
0 - 3 months	71 (52)	100
3 - 6 months	33 (24)	144
6 - 9 months	15 (11)	111
9 - 12 months	5 (4)	51
12 - 18 months	6 (4)	84
18 - 24 months	2 (1)	43
24 - 30 months	2 (1)	53
30 - 36 months	2 (1)	65

Note: This table is based on exposure information from the following studies: CA180002, CA180015, CA180035, CA180160 and CA180188.
The underlying study population consists of subjects with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.
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Table 4: **Duration of Dasatinib Exposure Totals in Adult Patients - Pooled Studies CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180056, CA180160, CA180188, and CA180363**

Duration of exposure	Persons N=2712 (%)	Person Time (months)
0 - 3 months	455 (17)	637
3 - 6 months	289 (11)	1268
6 - 9 months	204 (8)	1517
9 - 12 months	157 (6)	1638
12 - 18 months	215 (8)	3231
18 - 24 months	166 (6)	3507
24 - 30 months	232 (9)	6159
30 - 36 months	121 (4)	3993
36 - 48 months	162 (6)	6829
48 - 60 months	121 (4)	6645
60 - 72 months	258 (10)	16746
72 - 84 months	119 (4)	9372
84 - 96 months	163 (6)	14177
96 - 108 months	20 (<1)	2093
108 - 120 months	26 (<1)	2865
120 - 132 months	4 (<1)	510

Note: This table is based on exposure information from the following studies: CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180056, CA180160, CA180188, and CA180363.
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Table 5: Duration of Dasatinib Exposure Dose in Adult Patients with Newly Diagnosed Ph+ CP CML - Pooled Stuides CA180056 and CA180363

Dose of exposure	Persons N=324 (%)	Person Time (months)
100mg QD	324 (100)	14603

Note: This table is based on exposure information from the following studies: CA180056 and CA180363.
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Table 6: Duration of Dasatinib Exposure Dose in Adult Ph+ CML Patients with Resistance or Intolerance to Prior Therapy - Pooled Studies CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180160, and CA180188

Dose of exposure	Persons N=2252 (%)	Person Time (months)
100mg QD	224 (10)	10833
140mg QD	430 (19)	11216
50mg BID	178 (8)	7043
70mg BID	1371 (61)	35265
Other	49 (2)	1579

Note: This table is based on exposure information from the following studies: CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180160, and CA180188. The underlying study population consists of subjects with Chronic, Accelerated or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
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Table 7: **Duration of Dasatinib Exposure Dose in Adult Ph+ ALL Patients with Resistance or Intolerance to Prior Therapy - Pooled Studies CA180002, CA180015, CA180035, CA180160 and CA180188**

Dose of exposure	Persons N=136 (%)	Person Time (months)
140mg QD	40 (29)	188
70mg BID	93 (68)	455
Other	3 (2)	6

Note: This table is based on exposure information from the following studies: CA180002, CA180015, CA180035, CA180160 and CA180188. The underlying study population consists of subjects with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2016/val/rpt/adults/rmp_phall_v1.sas RUN DATE: 16-JUN-2016 9:21

Table 8: Duration of Dasatinib Exposure Dose in Adult Patients - Pooled Studies CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180056, CA180160, CA180188, and CA180363

Dose of exposure	Persons N=2712 (%)	Person Time (months)
100mg QD	548 (20)	25436
140mg QD	470 (17)	11404
50mg BID	178 (7)	7043
70mg BID	1464 (54)	35720
Other	52 (2)	1586

Note: This table is based on exposure information from the following studies: CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180056, CA180160, CA180188, and CA180363.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2016/val/rpt/adults/rmp_tot_v1.sas RUN DATE: 16-JUN-2016 9:21

Table 9: Dasatinib Exposure by Age Group And Gender in Adult Patients with Newly Diagnosed Ph+ CP CML - Pooled Studies CA180056 and CA180363

Age Group (years)	Persons		Person Time (months)	
	Male N = 183 (%)	Female N = 141 (%)	Male	Female
< 21	3 (2)	3 (2)	195	146
21 - 45	87 (48)	63 (45)	4228	2845
46 - 65	76 (42)	62 (44)	3131	2925
66 - 75	12 (7)	9 (6)	419	394
> 75	5 (3)	4 (3)	165	156

Note: This table is based on exposure information from the following studies: CA180056 and CA180363.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2016/val/rpt/adults/rmp_diag_v1.sas RUN DATE: 16-JUN-2016 9:21

Table 10: Dasatinib Exposure by Age Group And Gender in Adult Ph+ CML Patients with Resistance or Pooled Studies CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180160, and CA180188

Age Group (years)	Persons		Person Time (months)	
	Male N = 1187 (%)	Female N = 1065 (%)	Male	Female
< 21	15 (1)	7 (<1)	214	259
21 - 45	392 (33)	280 (26)	12564	9742
46 - 65	535 (45)	529 (50)	15563	16241
66 - 75	198 (17)	211 (20)	4775	5100
> 75	47 (4)	38 (4)	684	794

Note: This table is based on exposure information from the following studies: CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180160, and CA180188. The underlying study population consists of subjects with Chronic, Accelerated or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2016/val/rpt/adults/rmp_cml_v1.sas RUN DATE: 16-JUN-2016 9:21

Table 11: Dasatinib Exposure by Age Group And Gender in Adult Ph+ ALL Patients with Resistance or Intolerance to Prior Therapy - Pooled Studies CA180002, CA180015, CA180035, CA180160 and CA180188

Age Group (years)	Persons		Person Time (months)	
	Male N = 73 (%)	Female N = 63 (%)	Male	Female
< 21	6 (8)	0	46	0
21 - 45	24 (33)	23 (37)	79	154
46 - 65	28 (38)	27 (43)	146	95
66 - 75	13 (18)	11 (17)	77	42
> 75	2 (3)	2 (3)	10	2

Note: This table is based on exposure information from the following studies: CA180002, CA180015, CA180035, CA180160 and CA180188.
The underlying study population consists of subjects with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2016/val/rpt/adults/rmp_phall_v1.sas RUN DATE: 16-JUN-2016 9:21

Table 12: Exposure by Age Group And Gender in Adult Patients - Pooled Studies CA180002, CA180005, CA180006, CA180013, CA180015,CA180017, CA180034, CA180035, CA180039, CA180056, CA180160, CA180188, and CA180363)

Age Group (years)	Persons		Person Time (months)	
	Male N = 1443 (%)	Female N = 1269 (%)	Male	Female
< 21	24 (2)	10 (<1)	454	405
21 - 45	503 (35)	366 (29)	16870	12741
46 - 65	639 (44)	618 (49)	18841	19260
66 - 75	223 (15)	231 (18)	5270	5537
> 75	54 (4)	44 (3)	859	952

Note: This table is based on exposure information from the following studies: CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180056, CA180160, CA180188, and CA180363.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2016/val/rpt/adults/rmp_tot_v1.sas RUN DATE: 16-JUN-2016 9:21

Table 13: Dasatinib Exposure by Ethnic or Racial Origin in Adult Patients with Newly Diagnosed Ph+ CP CML - Pooled Studies CA180056 and CA180363

Ethnic/racial origin	Persons N=324 (%)	Person Time (months)
WHITE	196 (60)	8397
BLACK/AFRICAN AMERICAN	2 (<1)	125
ASIAN	108 (33)	5171
OTHER	18 (6)	910

Note: This table is based on exposure information from the following studies: CA180056 and CA180363.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2016/val/rpt/adults/rmp_diag_v1.sas RUN DATE: 16-JUN-2016 9:21

Table 14: Dasatinib Exposure by Ethnic or Racial Origin in Adult Ph+ CML Patients with Resistance or Intolerance to Prior Therapy - Pooled Studies CA180002, CA180005, CA180006, CA180013, CA180015,CA180017, CA180034, CA180035, CA180039, CA180160, and CA180188

Ethnic/racial origin	Persons N=2252(%)	Person Time (months)
WHITE	1726 (77)	49002
BLACK/AFRICAN AMERICAN	120 (5)	3127
ASIAN	327 (15)	11187
OTHER	68 (3)	2353
AMERICAN INDIAN/ALASKA NATIVE	1 (<1)	40
NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER	1 (<1)	0
UNAVAILABLE	9 (<1)	228

Note: This table is based on exposure information from the following studies: CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180160, and CA180188. The underlying study population consists of subjects with Chronic, Accelerated or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2016/val/rpt/adults/rmp_cml_v1.sas RUN DATE: 16-JUN-2016 9:21

Table 15: Dasatinib Exposure by Ethnic or Racial Origin in Adult Ph+ ALL Patients with Resistance or Intolerance to Prior Therapy - Pooled Studies CA180002, CA180015, CA180035, CA180160 and CA180188

Ethnic/racial origin	Persons N=136(%)	Person Time (months)
WHITE	120 (88)	586
BLACK/AFRICAN AMERICAN	3 (2)	2
ASIAN	7 (5)	47
OTHER	5 (4)	13
UNAVAILABLE	1 (<1)	1

Note: This table is based on exposure information from the following studies: CA180002, CA180015, CA180035, CA180160 and CA180188.
The underlying study population consists of subjects with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2016/val/rpt/adults/rmp_phall_v1.sas RUN DATE: 16-JUN-2016 9:21

Table 16: Dasatinib Exposure by Ethnic or Racial Origin in Adult Patients - Pooled Studies CA180002, CA180005, CA180006, CA180013, CA180015,CA180017, CA180034, CA180035, CA180039, CA180056, CA180160, CA180188, and CA180363

Ethnic/racial origin	Persons N=2712(%)	Person Time (months)
WHITE	2042 (75)	57985
BLACK/AFRICAN AMERICAN	125 (5)	3254
ASIAN	442 (16)	16404
OTHER	91 (3)	3276
AMERICAN INDIAN/ALASKA NATIVE	1 (<1)	40
NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER	1 (<1)	0
UNAVAILABLE	10 (<1)	229

Note: This table is based on exposure information from the following studies: CA180002, CA180005, CA180006, CA180013, CA180015, CA180017, CA180034, CA180035, CA180039, CA180056, CA180160, CA180188, and CA180363.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2016/val/rpt/adults/rmp_tot_v1.sas RUN DATE: 16-JUN-2016 9:21

Table 17: Duration of Dasatinib Exposure in Pediatric Patients, Dasatinib Mono-therapy - Pooled Studies CA180018 and CA180226

Duration of exposure	Persons N=188 (%)	Person Time (months)
0 - 3 months	44 (23)	50
3 - 6 months	13 (7)	57
6 - 9 months	7 (4)	51
9 - 12 months	8 (4)	85
12 - 18 months	7 (4)	107
18 - 24 months	7 (4)	155
24 - 30 months	18 (10)	478
30 - 36 months	13 (7)	441
36 - 48 months	12 (6)	517
48 - 60 months	40 (21)	2156
60 - 72 months	8 (4)	526
72 - 84 months	8 (4)	608
84 - 96 months	2 (1)	177
96 - 108 months	1 (1)	100

Note: This table is based on exposure information from the following studies: CA180018 and CA180226.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2017/val/rpt/pediatric/cumexp_v1.sas RUN DATE: 09-FEB-2017 10:06

Table 18: Duration of Dasatinib Exposure in Pediatric Patients, Dasatinib added to Chemo-therapy - CA180372

Duration of exposure	Persons N=106 (%)	Person Time (months)
0 - 3 months	1 (1)	2
3 - 6 months	10 (9)	50
6 - 9 months	4 (4)	31
9 - 12 months	5 (5)	54
12 - 18 months	20 (19)	312
18 - 24 months	58 (55)	1310
24 - 30 months	8 (8)	194

Note: This table is based on exposure information from study CA180372.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2016/val/rpt/pediatric/cumexp_v2_372.sas RUN DATE: 16-JUN-2016 10:11

Table 19: Duration of Dasatinib Exposure in Pediatric Patients, Dasatinib Mono-therapy - Pooled Studies CA180018 and CA180226

Dose of exposure	Persons N=188 (%)	Person Time (months)
60 mg/m^2	105 (56)	4147
80 mg/m^2	38 (20)	468
100 mg/m^2	6 (3)	8
120 mg/m^2	6 (3)	3
72 mg/m^2 (PFOS) (b)	33 (18)	882

Note:This table is based on exposure information from the following studies: CA180018 and CA180226.
(b) Powder for oral solution.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2017/val/rpt/pediatric/rmp_v1.sas RUN DATE: 09-FEB-2017 10:06

Table 20: Duration of Dasatinib Exposure in Pediatric Patients, Dasatinib added to Chemo-therapy - CA180372

Dose of exposure	Persons N=106(%)	Person Time (months)
60 mg/m^2	106 (100)	1953

Note: This table is based on exposure information from study CA180372.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2016/val/rpt/pediatric/rmp_v1_372.sas RUN DATE: 16-JUN-2016 10:11

Table 21: Dasatinib Exposure by Age Group And Gender in Pediatric Patients, Dasatinib Mono-therapy - Pooled Studies CA180018 and CA180226

Age Group (years)	Persons		Person Time (months)	
	Male N = 105 (%)	Female N = 83 (%)	Male	Female
< 2	1 (1)	4 (5)	36	145
2 - 11	50 (48)	37 (45)	1401	855
12 - 17	54 (51)	39 (47)	1554	1416
> 17	0	3 (4)	0	100

Note:This table is based on exposure information from the following studies: CA180018 and CA180226.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2017/val/rpt/pediatric/rmp_v1.sas RUN DATE: 09-FEB-2017 10:06

Table 22: Dasatinib Exposure by Age Group And Gender in Pediatric Patients, Dasatinib added to Chemo-therapy - CA180372

Age Group (years)	Persons		Person Time (months)	
	Male N = 57 (%)	Female N = 49 (%)	Male	Female
< 2	2 (4)	2 (4)	47	48
2 - 11	34 (60)	33 (67)	681	600
12 - 17	21 (37)	14 (29)	374	205
> 17	0	0	0	0

Note: This table is based on exposure information from study CA180372.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2016/val/rpt/pediatric/rmp_v1_372.sas RUN DATE: 16-JUN-2016 10:11

Table 23: Dasatinib Exposure by Ethnic or Racial Origin in Pediatric Patients, Dasatinib Mono-therapy - Pooled Studies CA180018 and CA180226

Ethnic/racial origin	Persons N=188 (%)	Person Time (months)
WHITE	141 (75)	3884
BLACK/AFRICAN AMERICAN	7 (4)	169
ASIAN	35 (19)	1357
OTHER	4 (2)	42
AMERICAN INDIAN/ALASKA NATIVE	1 (1)	56

Note:This table is based on exposure information from the following studies: CA180018 and CA180226.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2017/val/rpt/pediatric/rmp_v1.sas RUN DATE: 09-FEB-2017 10:06

Table 24: **Dasatinib Exposure by Ethnic or Racial Origin in Pediatric Patients, Dasatinib added to Chemo-therapy - CA180372**

Ethnic/racial origin	Persons N=106 (%)	Person Time (months)
WHITE	80 (75)	1504
BLACK/AFRICAN AMERICAN	12 (11)	212
ASIAN	4 (4)	75
AMERICAN INDIAN/ALASKA NATIVE	1 (1)	10
NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER	1 (1)	2
OTHER	8 (8)	150

Note: This table is based on exposure information from study CA180372.
PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/rmp/2016/val/rpt/pediatric/rmp_v1_372.sas RUN DATE: 16-JUN-2016 10:11

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

1 page(s) excluding cover page

ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

TABLE OF CONTENTS

Adverse Event Report Questionnaire

AWARE #: [redacted]

PLEASE PROVIDE THE INFORMATION CHECKED (X) BELOW FOR THE REPORTED ADVERSE EVENT(S):

1. Patient's date of birth or age: Gender:
2. Please provide suspect product(s) those product(s) that are suspected to be associated with one or more adverse events:
3. Daily dose of the suspect product(s): and regimen:
4. Route of administration:
5. Indication(s) for which the suspect product(s) was (were) prescribed:
6. Starting and stop dates of treatment/ treatment duration:
7. Lot/Batch number(s) and Expiration date(s)
8. Provide any other suspect medications, not listed above, that may have contributed to the occurrence of the adverse event (s), including indication for which they were prescribed and treatment dates:
9. Please provide details of adverse event(s):
    a. Start date if known:
    b. Time lag if adverse event(s) occurred after cessation of treatment with the suspect product(s):
    c. Signs and symptoms in chronological order:
10. Diagnostic tests (provide test names, dates, results and normal ranges (include units) as well as pre-treatment results if available):
11. Final diagnosis:
12. Did the event require hospitalization? If yes, specify which event
13. Treatment of adverse event(s):

14. Adverse event(s) stop date and outcome (information on recovery and sequelae, if any):

15. For fatal outcome, please provide cause of death and a comment on its possible relationship to the suspect product(s):

16. Did the adverse event(s) abate after use stopped or dose reduced (if applicable)?

17. Did the adverse event(s) reappear after re-introduction of the suspect product(s) (if applicable)?

18. Please provide causal relationship assessment between the suspect product(s) and adverse event(s):

19. Please list any concomitant medications:

    a. Medication name, daily dose/regimen, indication; start/stop date and time or duration

20. Are there any other etiological factors: relevant medical and/or drug history (please specify), family history (please specify) and drug/alcohol/tobacco abuse if applicable:

21. Additional questions:

- Did the patient have past history of HBV or other hepatitis viral infection?
- Please provide baseline LFT, HBV DNA levels and HBV serology, including HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc.
- Please provide LFT, HBV DNA and HBV serology data collected during the event.
- Please provide details regarding the hepatitis B treatment medication, duration and treatment outcome.
- Did the patient have concurrent use of any immunosuppressant, such as rituximab or ofatumumab?
- Did the patient ever use any other tyrosine kinase inhibitor such as Imantinib prior to the event?

Health Practitioner Name (Print)

Health Practitioner Name (Signature)

Dasatinib Pulmonary Hypertension (PH) Follow-Up Form

4000

Bristol-Myers Squibb Company

Research and Development

CLINICAL CASE REPORT

PULMONARY HYPERTENSION

PROTOCOL NO. **CA180372**

INVESTIGATOR (PLEASE PRINT)

SITE NUMBER	SUBJECT NUMBER
☐☐☐☐	☐☐☐☐☐

COVER005

Bristol-Myers Squibb Company **Pulmonary Hypertension** Page 4000.1

PROTOCOL	SITE NUMBER	SUBJECT NUMBER	
CA180372			BLANK?
SUBEVENT#		VISIT CODE	PH_ _

EVENT IDENTIFICATION

CSPHD001-PL5127

PULMONARY HYPERTENSION

☐ NSAE

☐ SAE

Adverse Event Clinical Diagnosis (Verbatim Term)

Date of Onset
DD-MMM-YYYY

Added page Jan 2012

Bristol-Myers Squibb Company **Pulmonary Hypertension** Page 4001

PROTOCOL	SITE NUMBER	SUBJECT NUMBER	
CA180372			BLANK?
SUBEVENT#		VISIT CODE	PH_ _

PRESENTING SIGNS AND SYMPTOMS OF PH

SIGNS004
Page 1 of 2

Complete for all subjects. Do not mark this page as blank.

Signs and Symptoms: DYSPNEA
Symptoms?: ☐ NO ☐ YES ☐ UNKNOWN
Specify *Do Not Enter*:

Signs and Symptoms: PERIPHERAL EDEMA
Symptoms?: ☐ NO ☐ YES ☐ UNKNOWN
Specify *Do Not Enter*:

Signs and Symptoms: ABDOMINAL PAIN
Symptoms?: ☐ NO ☐ YES ☐ UNKNOWN
Specify *Do Not Enter*:

Signs and Symptoms: FATIGUE
Symptoms?: ☐ NO ☐ YES ☐ UNKNOWN
Specify *Do Not Enter*:

Signs and Symptoms: SYNCOPE
Symptoms?: ☐ NO ☐ YES ☐ UNKNOWN
Specify *Do Not Enter*:

Bristol-Myers Squibb Company **Pulmonary Hypertension** Page 4001

PROTOCOL	SITE NUMBER	SUBJECT NUMBER	
CA180372			BLANK?
SUBEVENT#		VISIT CODE	PH_ _

PRESENTING SIGNS AND SYMPTOMS OF PH

SIGNS004
Page 2 of 2

Signs and Symptoms: CHEST PAIN
Symptoms?: ☐ NO ☐ YES ☐ UNKNOWN
Specify *Do Not Enter*:

Signs and Symptoms: WEAKNESS
Symptoms?: ☐ NO ☐ YES ☐ UNKNOWN
Specify *Do Not Enter*:

Signs and Symptoms: OTHER
Symptoms?: ☐ NO ☐ YES ☐ UNKNOWN
If Yes, Specify:

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PROTOCOL	SITE NUMBER	SUBJECT NUMBER	BLANK?
CA180372			

SUBEVENT#	VISIT CODE
	PH__

2D ECHOCARDIOGRAM

SRELPROC012-EX4626

Was 2D echocardiogram performed? ☐ NO ☐ YES *If yes, complete below*

Date 2D echocardiogram was performed DD-MMM-YYYY

Left ventricular ejection fraction %

Interpretation of 2D echocardiogram valvular assessment
☐ NORMAL
☐ ABNORMAL

Mean PAP nn mmHg

Mean Systolic PAP nn mmHg

Mean Diastolic PAP nn mmHg

Tricuspid Regurgitation Velocity nn m/sec

Bristol-Myers Squibb Company **Pulmonary Hypertension** Page 4003

PROTOCOL	SITE NUMBER	SUBJECT NUMBER	
CA180372			BLANK?
SUBEVENT#		VISIT CODE	PH__

STUDY RELATED PROCEDURES

Complete for all subjects. Do not mark this page as blank.

SRELPROC001
Page 1 of 2

Procedure: CHEST X-RAY
Location:

Was Procedure Performed? ☐ NO ☐ YES
Date DD-MMM-YYYY:
Interpretation ☐ NORMAL ☐ ABNORMAL

If Abnormal, Record Findings:

Procedure: POLYSOMNOGRAM
Location:

Was Procedure Performed? ☐ NO ☐ YES
Date DD-MMM-YYYY:
Interpretation ☐ NORMAL ☐ ABNORMAL

If Abnormal, Record Findings:

Procedure: OVERNIGHT OXIMETRY
Location:

Was Procedure Performed? ☐ NO ☐ YES
Date DD-MMM-YYYY:
Interpretation ☐ NORMAL ☐ ABNORMAL

If Abnormal, Record Findings:

Bristol-Myers Squibb Company **Pulmonary Hypertension** Page 4003

PROTOCOL	SITE NUMBER	SUBJECT NUMBER	
CA180372			BLANK?
SUBEVENT#		VISIT CODE	PH__

STUDY RELATED PROCEDURES

SRELPROC001
Page 2 of 2

Procedure PULMONARY ANGIOGRAM

Location

Was Procedure Performed?
☐ NO
☐ YES

Date DD-MMM-YYYY

Interpretation
☐ NORMAL
☐ ABNORMAL

If Abnormal, Record Findings

Procedure CHEST CT SCAN

Location

Was Procedure Performed?
☐ NO
☐ YES

Date DD-MMM-YYYY

Interpretation
☐ NORMAL
☐ ABNORMAL

If Abnormal, Record Findings

Bristol-Myers Squibb Company **Pulmonary Hypertension** Page 4004

PROTOCOL	SITE NUMBER	SUBJECT NUMBER	
CA180372			BLANK?
SUBEVENT#		VISIT CODE	PH__

6 MINUTE WALK TEST

SRELPROC024-PL4651

Was test performed? NO YES *If yes, complete below*

DD-MMM-YYYY

Date of exam

Distance walked FEET METERS

Dyspnea on exertion *(Borg scale 0-10 point)*

O2 SATURATION AT START

%

O2 SATURATION LOWEST RECORDED

%

OXYGEN DELIVERY RATE

l/min

Bristol-Myers Squibb Company **Pulmonary Hypertension** Page 4005

PROTOCOL	SITE NUMBER	SUBJECT NUMBER	BLANK?
CA180372			

SUBEVENT# | VISIT CODE PH__

SRELPROC024

PULMONARY FUNCTION TEST

SPIROMETRY

Was spirometry test performed? ☐ NO ☐ YES *If yes, complete below*

DD-MMM-YYYY

Date of exam

FVC

n.nn

L

FEV1

n.nn

L

TLC

n.nn

L

FRC

n.nn

L

DLCO

Was DLCO test performed? ☐ NO ☐ YES *If yes, complete below*

DD-MMM-YYYY

Date of exam

DLCO

nn.nn

mL/min/mmHg

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PROTOCOL	SITE NUMBER	SUBJECT NUMBER	BLANK?
CA180372			

SUBEVENT# | VISIT CODE PH__

RIGHT HEART CATHETERIZATION

LABMISC011
Page 1 of 2

Do not include additional details such as comments with the responses.
Enter a zero (0) only if it is a measured test result.

Were any of the following protocol specified activities performed?

☐ NO ☐ YES *If yes, complete below*

Date of collection DD-MMM-YYYY

MEAN PAP

Result	Unit
	mmHg

SYSTOLIC PAP

Result	Unit
	mmHg

DIASTOLIC PAP

Result	Unit
	mmHg

PULMONARY CAPILLARY WEDGE PRESSURE

Result	Unit
	mmHg

RIGHT ATRIAL PRESSURE

Result	Unit
	mmHg

RIGHT VENTRICULAR PRESSURE

Result	Unit
	mmHg

CARDIAC OUTPUT

Result	Unit
	L/min

CARDIAC INDEX

Result	Unit
	L/min

Bristol-Myers Squibb Company **Pulmonary Hypertension** Page 4006

PROTOCOL	SITE NUMBER	SUBJECT NUMBER	BLANK?
CA180372			

SUBEVENT#	VISIT CODE
	PH_ _

RIGHT HEART CATHETERIZATION

LABMISC011
Page 2 of 2

Do not include additional details such as comments with the responses.
Enter a zero (0) only if it is a measured test result.

MIXED VENOUS OXYGEN SATURATION (SvO2)

Result	Unit
	%

PULMONARY VASCULAR RESISTANCE

Result	Unit
	mmHg/L/min

Bristol-Myers Squibb Company **Pulmonary Hypertension** Page 4007

PROTOCOL	SITE NUMBER	SUBJECT NUMBER	BLANK?
CA180372			

SUBEVENT#	VISIT CODE
	PH_ _

VASOREACTIVITY

SRELPROC016-PL4652

Was vasoreactivity performed? ☐ NO ☐ YES *If yes, complete below*

Date performed DD-MMM-YYYY

Agent

Vasodilation present? ☐ NO ☐ YES

Bristol-Myers Squibb Company **Pulmonary Hypertension** Page 4008

PROTOCOL	SITE NUMBER	SUBJECT NUMBER	
CA180372			BLANK?
SUBEVENT#		VISIT CODE	PH__

VENTILATION/PERFUSION SCAN

SRELPROC016-EX4627

Was ventilation/perfusion scan? ☐ NO ☐ YES *If yes, complete below*

Date of procedure DD-MMM-YYYY

Interpretation
☐ NORMAL
☐ ABNORMAL

Was there a V/Q mismatch?
☐ NO
☐ YES

If yes, describe V/Q mismatch

Bristol-Myers Squibb Company **Pulmonary Hypertension** Page 4009

PROTOCOL	SITE NUMBER	SUBJECT NUMBER	
CA180372	☐☐☐☐☐	☐☐☐☐☐	BLANK? ☐
SUBEVENT# ☐		VISIT CODE PH__	

MEDICAL TREATMENT PROCEDURES FOR PH

CSPPROC001

Did the subject receive medical treatment procedures for PH?

☐ NO ☐ YES *If yes, complete below*

Procedure *(Specify one per row)*
Ensure these procedures are also recorded on the appropriate procedure CRF pages

Bristol-Myers Squibb Company **Pulmonary Hypertension** Page 4010

PROTOCOL	SITE NUMBER	SUBJECT NUMBER	BLANK?
CA180372			

SUBEVENT#	VISIT CODE
	PH_ _

REVISED WHO CLASSIFICATION OF PULMONARY HYPERTENSION

DZASMT001-PL4708

Was the revised WHO classification used to assess pulmonary hypertension? ☐ NO ☐ YES *If yes, complete below*

Date of assessment DD-MMM-YYYY

Revised WHO class

- ☐ CLASS 1 (PULMONARY ARTERIAL HYPERTENSION (PAH))
- ☐ CLASS 2 (PULMONARY HYPERTENSION WITH LEFT HEART DISEASE)
- ☐ CLASS 3 (PULMONARY HYPERTENSION ASSOCIATED WITH LUNG DISEASE AND/OR HYPOXEMIA)
- ☐ CLASS 4 (PULMONARY HYPERTENSION DUE TO CHRONIC THROMBOTIC AND/OR EMBOLIC DISEASE (CTEPH))
- ☐ CLASS 5 (MISCELLANEOUS)

Revised page Feb 2012

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PROTOCOL	SITE NUMBER	SUBJECT NUMBER	BLANK?
CA180372			

SUBEVENT#	VISIT CODE
	PH__

RISK FACTORS FOR PH

RISKFACT001
Page 1 of 4

Does the subject have any of the risk factors for PH listed below?

☐ NO ☐ YES ☐ UNKNOWN *If yes, complete below*

Risk Factor	Risk Factor Present?	Onset Date of Most Recent Occurrence DD-MMM-YYYY
CONNECTIVE TISSUE DISEASE	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	Risk Factor Present?	Onset Date of Most Recent Occurrence DD-MMM-YYYY
HIV INFECTION	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	Risk Factor Present?	Onset Date of Most Recent Occurrence DD-MMM-YYYY
CHRONIC LIVER DISEASE	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	Risk Factor Present?	Onset Date of Most Recent Occurrence DD-MMM-YYYY
SCHISTOSOMIASIS	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

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PROTOCOL	SITE NUMBER	SUBJECT NUMBER	BLANK?
CA180372			

SUBEVENT# | VISIT CODE PH__

RISK FACTORS FOR PH

RISKFACT001
Page 2 of 4

Risk Factor	Risk Factor Present?	Onset Date of Most Recent Occurrence DD-MMM-YYYY
PULMONARY CAPILLARY HEMANGIOMATOSIS	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	Risk Factor Present?	Onset Date of Most Recent Occurrence DD-MMM-YYYY
CARDIAC CONDITIONS	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	Risk Factor Present?	Onset Date of Most Recent Occurrence DD-MMM-YYYY
LUNG DISEASE	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	Risk Factor Present?	Onset Date of Most Recent Occurrence DD-MMM-YYYY
HEMATOLOGIC DISORDERS	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

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PROTOCOL	SITE NUMBER	SUBJECT NUMBER	BLANK?
CA180372			

SUBEVENT# | VISIT CODE PH__

RISK FACTORS FOR PH

RISKFACT001
Page 3 of 4

Risk Factor	Risk Factor Present?	Onset Date of Most Recent Occurrence DD-MMM-YYYY
SYSTEMIC DISORDERS	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	Risk Factor Present?	Onset Date of Most Recent Occurrence DD-MMM-YYYY
METABOLIC DISORDERS	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	Risk Factor Present?	Onset Date of Most Recent Occurrence DD-MMM-YYYY
CHRONIC RENAL FAILURE	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Risk Factor	Risk Factor Present?	Onset Date of Most Recent Occurrence DD-MMM-YYYY
TUMORAL OBSTRUCTION	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

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PROTOCOL	SITE NUMBER	SUBJECT NUMBER	
CA180372			BLANK?
SUBEVENT#		VISIT CODE	PH_ _

RISK FACTORS FOR PH

RISKFACT001
Page 4 of 4

Risk Factor	Risk Factor Present?	Onset Date of Most Recent Occurrence DD-MMM-YYYY
SUBSTANCE ABUSE	☐ NO ☐ YES ☐ UNKNOWN	

Specify Risk Factor Details

Bristol-Myers Squibb Company **Pulmonary Hypertension** Page 4012

PROTOCOL	SITE NUMBER	SUBJECT NUMBER	
CA180372			BLANK?
SUBEVENT#		VISIT CODE	PH_ _

SUSPECT MEDICATION FOR PH

CSPMED001

Did subject receive suspect medication for PH?

NO YES *If yes, complete below*

Medication *(List one per row)*

Use generic name whenever possible; use brand name for combination product.
Ensure these medications are also recorded on the appropriate concomitant medication CRF pages.

** Pulmonary Arterial Hypertension **
** Additional Lab Data Instruction **

Note: Only prepare and submit the Lab Requisition page to report additional lab tests performed in relation to PH events. We are specifically interested in the following results:

Category	Test Code	Test Description
HEMATOLOGY	HB	Hemoglobin
HEMATOLOGY	HCT	Hematocrit
HEMATOLOGY	RBC	RBC
HEMATOLOGY	PLAT	Platelet Count
HEMATOLOGY	WBC	WBC
HEMATOLOGY	NEUT	Neutrophils
HEMATOLOGY	BANDS	Bands
HEMATOLOGY	LYMPH	Lymphocytes
HEMATOLOGY	MONOS	Monocytes
HEMATOLOGY	BASO	Basophils
HEMATOLOGY	EOS	Eosinophils
HEMATOLOGY	BLAST	Blasts
HEMATOLOGY	MYELO	Myelocytes
HEMATOLOGY	META	Metamyelocytes
HEMATOLOGY	PROMY	Promyelocytes
HEMATOLOGY	Other	
HEMATOLOGY	Other	
HEMATOLOGY	HGBA1	Hemoglobin A1
HEMATOLOGY	HGBA2	Hemoglobin A2
HEMATOLOGY	HGBF	Hemoglobin F
HEMATOLOGY	HGBS	Hemoglobin G
HEMATOLOGY	Other	
HEMATOLOGY	Other	
CHEMISTRY	AST	AST (SGOT)
CHEMISTRY	ALT	ALT (SGPT)
CHEMISTRY	TBILI	Total Bilirubin
CHEMISTRY	ALP	Alkaline Phosphatase
CHEMISTRY	BUN/Urea	Blood Urea Nitrogen (BUN)
CHEMISTRY	CREAT	Creatinine
CHEMISTRY	NA	Sodium
CHEMISTRY	K	Potassium
CHEMISTRY	CL	Chloride
CHEMISTRY	FT4	Free T4
CHEMISTRY	T3	T3
CHEMISTRY	TSH	TSH
CHEMISTRY	APO2	Partial Pressure O2

** Pulmonary Arterial Hypertension **
** Additional Lab Data Instruction **

Note: Only prepare and submit the Lab Requisition page to report additional lab tests performed in relation to PH events. We are specifically interested in the following results:

CHEMISTRY	APCO2	Partial Pressure CO2
CHEMISTRY	APH	Ph
CHEMISTRY	HCO3	Bicarbonate
CHEMISTRY	ASO2	O2 Saturation
CHEMISTRY	BNP	B-type Natriuretic Peptide
COAGULATION	PTTH	PTT Heparin Neutralized
COAGULATION	PTT1	PTT Time 1:1 mix
COAGULATION	PLATN	Platelet neutralization
COAGULATION	HPN	Hexagonal Phospholipid Neutralizaton
COAGULATION	RT	Reptilase Time
COAGULATION	DRVVT	Dilute Russell Viper Venom Time
COAGULATION	DRVV1	Dilute Russell Viper Venom Time 1:1 Mix
COAGULATION	DRVVC	Dilute Russell Viper Venom Time, Confirm
COAGULATION	Other	
IMMUNOLOGY	ANA	Antinuclear Antibody
IMMUNOLOGY	ANCA	Antineutrophil cytoplasmic antibody
IMMUNOLOGY	RF	Rheumatoid Factor
IMMUNOLOGY	ESR	Erythrocyte Sedimentation Rate
IMMUNOLOGY	SCL70	Anti-topoisomerase1, Anti-SCL-70
IMMUNOLOGY	CMIGG	Centromere Antibody, IgG
IMMUNOLOGY	ARP3	Anti-RNA polymerase III
IMMUNOLOGY	B2GPA	Anti-beta2-glycoprotein1 - IGA
IMMUNOLOGY	B2GPG	Anti-beta2-glycoprotein1 - IGG
IMMUNOLOGY	B2GPM	Anti-beta2-glycoprotein1 - IGM
IMMUNOLOGY	DDNAQ	Anti-double stranded DNA antibodies - Quantitative
IMMUNOLOGY	DSDNA	Anti-double stranded DNA antibodies - Qualitative
IMMUNOLOGY	ACAB	Anti-cardiolipin antibodies
IMMUNOLOGY	ACIGA	Anti-cardiolipin antibodies IGA
IMMUNOLOGY	ACIGG	Anti-cardiolipin antibodies IGG
IMMUNOLOGY	ACIGM	Anti-cardiolipin antibodies IGM
IMMUNOLOGY	APAG	Antiphospholipid antibody IGG
IMMUNOLOGY	APAM	Antiphospholipid antibody IGM
IMMUNOLOGY	HIVS	HIV Screen

** Pulmonary Arterial Hypertension Data Requisition **

Bristol-Myers Squibb - ICON Central Laboratories
123 Smith Street, Farmingdale New York 11735 Email Icon-Iris@iconplc.com Tel:631-306-9650

Note: Only prepare and submit this page to report tests performed in relation to PH events.

PROTOCOL NUMBER	CA180-372	**SITE NUMBER**	__ __ __ __
SUBJECT NUMBER	__ __ __ __ __	**DATE OF BIRTH**	__ __ - __ __ __ - __ __ __ __ (D D M M M Y Y Y Y)
GENDER AT BIRTH	☐ Male ☐ Female	**Number of Pages for this Subject** (Including cover page):	

Document Preparation:

1. **Only prepare and submit this page for Pulmonary Arterial Hypertension (PH) test(s) as per BMS Guidelines.**
2. Complete this requisition form by filling in information for visit(s) being sent (include total pages).
3. Write the **Site Number and Subject Number** on the **TOP** of **EACH** page of the final lab report.
4. Write the **Lab Name and Address (in English)** on the **TOP** of the final lab report if not present.

PH Event	*Collection Date (Example: 01 - Jan - 2006)*	*Collection Time (00:00 – 23:59)*	*Comment*
PH	__ __ - __ __ __ - __ __ __ __ (D D M M M Y Y Y Y)	__ __ : __ __	
PH 02	__ __ - __ __ __ - __ __ __ __ (D D M M M Y Y Y Y)	__ __ : __ __	
PH 03	__ __ - __ __ __ - __ __ __ __ (D D M M M Y Y Y Y)	__ __ : __ __	
PH 04	__ __ - __ __ __ - __ __ __ __ (D D M M M Y Y Y Y)	__ __ : __ __	
PH 05	__ __ - __ __ __ - __ __ __ __ (D D M M M Y Y Y Y)	__ __ : __ __	
PH __	__ __ - __ __ __ - __ __ __ __ (D D M M M Y Y Y Y)	__ __ : __ __	
PH __	__ __ - __ __ __ - __ __ __ __ (D D M M M Y Y Y Y)	__ __ : __ __	

Revised page Jan 2012

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

1 page(s) excluding cover page

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (IF APPLICABLE)

The Marketing Authorization Holder shall ensure that all physicians who are expected to prescribe dasatinib are provided with the following:

Physician educational material:

- The Summary of Product Characteristics
- Harmonisied Direct Healthcare Professional Communication (DHPC):
    - Commumication Plan: HBV Reactivation
    - Letter: HBV Reactivation

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Glivec® (imatinib) Sprycel® (dasatinib) Tasigna® (nilotinib) Bosulif® (bosutinib) Iclusig® (ponatinib)
Marketing authorisation holder(s)	Novartis Europharm Ltd. Bristol Myers Squibb Novartis Europharm Ltd. Pfizer Ltd. ARIAD Pharma Ltd.
Safety concern and purpose of the communication plan	Potential risk of hepatitis B reactivation in patients receiving BCR-ABL tyrosine kinase inhibitors (TKIs) (Glivec® (imatinib), Sprycel® (dasatinib), Tasigna® (nilotinib), Bosulif® (bosutinib) and Iclusig® (ponatinib). Raise awareness of this potential risk to the HCPs involved in the prescription and delivery of BCR-ABL TKIs.
DHPC recipients	1. Haemato-oncologists, haematologists, oncologists (for Glivec®) 2. Hospital chief pharmacists and oncology pharmacists
Member states where the DHPC will be distributed	All EU member states, Iceland and Norway

Timetable	
DHPC and communication plan (in English) agreed by PRAC	**22 February 2016**
DHPC and communication plan (in English) agreed by CHMP	**25 February 2016**
Submission of translated DHPCs to the national competent authorities for review	**03 March 2016**
Expected agreement of translations by national competent authorities	**28 March 2016**
Dissemination of DHPC letter	**11 April 2016**

DD-MM-2016

Direct Healthcare Professional Communication

BCR-ABL tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib, bosutinib, ponatinib) –Need to screen patients for hepatitis B virus before treatment due to risk of hepatitis B reactivation

Dear Healthcare Professional,

In agreement with the European Medicines Agency (EMA) and *<insert NCA>*, the undersigned Marketing Authorisation Holders would like to inform you of the following:

Summary:

Cases of Reactivation of hepatitis B virus (HBV) have occurred in patients who are chronic carriers of HBV after they received BCR-ABL tyrosine kinase inhibitors (TKIs). Some cases of HBV reactivation resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Recommendations:

- **Patients should be tested for HBV infection before initiating treatment with BCR-ABL TKIs.**
- **Consult experts in liver disease and in the treatment of HBV before treatment in patients with positive HBV serology (including those with active disease) is initiated and for patients who test positive for HBV infection during treatment.**
- **Closely monitor patients who are carriers of HBV requiring treatment with BCR-ABL TKIs for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy.**

Background on the safety concern and recommendations

A recent cumulative review of data from clinical trials and postmarketing experience has shown that HBV reactivation can occur in chronic HBV carriers, after they received BCR-ABL TKIs. Some of these cases included acute hepatic failure or fulminant hepatitis leading to liver transplantation or fatal outcome.

These case reports indicate that HBV reactivation may occur at any time during TKI treatment. Some of these patients had a documented history of hepatitis B, for other cases, the serologic status at baseline was not known. An increase in viral load or positive serology was diagnosed upon HBV reactivation.

HBV reactivation is considered a class-effect of BCR-ABL TKI, although the mechanism and the frequency of HBV reactivation during exposure is not known at this time.

As recommended by the European Medicines Agency (EMA) and National Competent Authorities, the summary of product characteristics (SmPC) and the package leaflet of all BCR-ABL TKIs will be updated to reflect the new safety information.

Call for reporting of adverse reactions

Healthcare professionals are reminded to continue to report suspected adverse reactions associated with these products in accordance with the national spontaneous reporting system. <Details of national reporting system to be included>.

When reporting please provide as much information as possible, including information about medical history, test results, any concomitant medication, onset and treatment dates.

Company contact point

If you have further questions or require additional information regarding *<COMPANIES NAMES>* products *<BRANDNAME DRUGS>*, please contact *<COMPANIES CONTACT DETAILS>*.

Yours sincerely,

<relevant (local) signatures>