NOVARTIS

Chief Medical Office & Patient Safety

Nilotinib

AMN107

EU Safety Risk Management Plan

Active substance (INN or common name):	Nilotinib
Product concerned (brand name):	Tasigna®
Document status:	Final
Version number:	25.0
Data lock point for this RMP	Clinical data cut-off: CAMN107A2203: 28-Aug-2020 Cut-off date for PSUR: 31-Jan-2020
Date of final sign off	18-May-2021

Template version 6.3, Effective from 24-Feb-2021

Rationale for submitting an updated RMP:

Compared to the effective European Union (EU) Risk Management Plan (RMP) version 23.0, this consolidated version of the RMP (version 25.0) reflects the changes of RMP version 24.0 which were submitted within variation application EMEA/H/C/000798/II/0109. The following were the updates made to EU RMP version 24.0:

- Removal of a missing information: "long-term follow-up in pediatric patients"
- Update to summarize the results of the completed additional pharmacovigilance activity Study CAMN107A2203.

As a reminder, the EU RMP version 24.0, which is currently under European Medicines Agency (EMA) review (Regulatory procedure number EMEA/H/C/000798/II/0109), has been written based on the previous effective EU RMP version 22.1 approved on 11-Jun-2020 (Regulatory procedure number EMEA/H/C/000798/II/0103).

Summary of significant changes in this RMP:

Compared to the previous EU RMP version 23.0 the version of the RMP (v 25.0) reflects the following changes.

Note: Some minor changes have been included in the version 25.0 to reflect the changes incorporated in the new Novartis RMP template v6.3 released on 24-Feb-2021. Those changes consist only of updates in a few header titles.

Part	Major changes in v 25.0 compared to the RMP v 23.0
Part I	Addition of a hyperlink to the product information to Proposed Summary of Product Characteristics (SmPC).
Part I Module SI	No change
Part II Module SII	No change.
Part II Module SIII	Update of the clinical trial exposure data.
Part II Module SIV	No change.
Part II Module SV	No change.
Part II Module SVI	No change.
Part II Module SVII	Updates to reflect the removal of the following missing information topics: Long-term follow-up in pediatric patients. Updated Table 8-7 to include the summary of safety findings from Study CAMN107A2203. All the risk tables were updated with information from Study CAMN107A2203 (including Table 8-6-clinical trial data of growth retardation). Updated Table 8-9 to reflect PSUR (31-Jan-2020) reproductive toxicity/pregnancy data.
Part II Module SVIII	Updated to reflect the current summary of safety concerns by removal of missing information 'Long-term follow-up in pediatric patients'.
Part III	Study CAMN107A2203 (category 3) is completed. It has been removed from this section.
Part IV	Study CAMN107A2203 is completed. It has been removed from this section.

Part	Major changes in v 25.0 compared to the RMP v 23.0
Part V	Update Table 12-1 and Table 12-2 to remove the missing information "Long-term follow-up in pediatric patients". Study CAMN107A2203 is completed. It has been removed from this section.
Part VI	Update Table 13-1 to reflect the new list of safety concerns. Removal of the following missing information topics: Long-term follow-up in pediatric patients. Study CAMN107A2203 is completed. It has been removed from this section.
Part VII	
Annex 1	Updated to reflect the new template requirements.
Annex 2	Study CAMN107A2203 is listed as a completed study (submission date of the clinical study report was provided).
Annex 3	No change.
Annex 4	No change.
Annex 5	The protocol of the Study CAMN107A2203 is removed as the study is now completed.
Annex 6	No change.
Annex 7	The [Brief Statistical Description portion and Supportive Outputs of Annex 7] and the Novartis internal references were updated
Annex 8	The table presenting the summary of changes to the RMP was updated.

Other RMP versions under evaluation

No RMP versions are currently under evaluation.

Details of the currently approved RMP:

Version number: 23.0

Approved with procedure: EMEA/H/C/000798/II/0107

Date of approval (opinion date): 11-Mar-2021

QPPV name: Dr. David Lewis

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

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List of abbreviations

ABL1	Abelson murine leukemia viral oncogene homolog 1
ADR	Adverse drug reaction
AE	Adverse event
AFP	Alpha-fetoprotein
AML	Acute myeloid leukemia
ALL	Acute lymphoblastic leukemia
allo-SCT	allogeneic hematopoietic stem-cell transplantation
ALT	Alanine aminotransferase
AP	Accelerated phase
AUC	Area Under the Curve
BC	Blast crisis
BCC	Basal cell carcinoma
BCR-ABL	Fusion gene from the breakpoint cluster region (BCR) gene in chromosome 22 and Abelson (ABL) gene in chromosome 9. The protein product from BCR-ABL oncogene is a tyrosine kinase
bFGF	basic fibroblast growth factor
BSI	Blood stream infections
CAT	Computed tomography scan
CDC	Centers for disease control
CI	Confidence interval
CML	Chronic Myelogenous Leukemia
CNS	Central Nervous System
CP	Chronic Phase
CSR	Clinical study report
CT	Computed tomography
CVD	Cerebrovascular disease
CVE	Cardiovascular Events
CYP	Cytochrome P450 Isoenzyme
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
EUROCAT	The European Surveillance of Congenital Anomalies
FCS	Fetal calf serum
FDA	Food and Drug Administration
GI	Gastrointestinal
GVP	Good pharmacovigilance practices
HCP	Health Care Professional
HLA	Human leukocyte antigen
HUVEC	Human Vascular Endothelial Cells
ICH	International Council for Harmonization
IFD	Invasive fungal disease
IR	Incidence rate
IS	International scale
JAK	Janus kinase receptor
LV	left ventricular

LPLV	Last patient last visit
MACDP	Metropolitan Atlanta Congenital Defects Program
MedDRA	Medical Dictionary for Regulatory Affairs
MR	Molecular response
MRI	Magnetic resonance imaging
MMR	Major molecular response
NMSC	Non-melanoma skin cancer
NOEL	No-Observable-Effect-Level
OATP	Organic anion-transporting polypeptides
OCT	Organic cation transporter
OR	Overall response
P-gp	P-Glycoprotein
Ph+	Philadelphia chromosome positive
PIP	Pediatric investigational plan
PK	Pharmacokinetics
PL	Package leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
PT	Preferred Term
PTY	Patient-years
PY	Person-years
QT	QT interval
QTcF	QT interval corrected by Fridericia's formulae
RMP	Risk management plan
SAE	Serious Adverse Event
SCC	Squamous cell carcinoma
SD	Standard deviation
SDS	Standard-Deviation Score
SIR	Standardized incidence ratio
SmPC	Summary of product characteristics
TFR	Treatment-free remission
TKI	Tyrosine kinase inhibitor
UGT1A1	Uridine 5' Diphospho-Glucuronosyltransferase
VEGF	Vascular endothelial growth factor

1 Part I: Product Overview

Table 1-1 Part I.1 - Product Overview

Active substance (INN or common name)	Nilotinib
Pharmacotherapeutic group (ATC Code)	L01XE08
Marketing Authorization Holder	Novartis Europharm Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Tasigna®
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class:** Tyrosine kinase inhibitor
	Summary of mode of action: Its mode of action is to selectively inhibit the TK activity of fusion gene from the breakpoint cluster region (BCR) gene in chromosome 22 and Abelson (ABL) gene in chromosome 9 (BCR-ABL). In addition to ABL kinases it inhibits, receptor kinases including the platelet-derived growth factor receptor (PDGFR), stem cell factor receptor (KIT), colony stimulating factor-1R (CSF-1R), discoidin domain receptor (DDR), and ephrin (e.g. EphB4) receptor kinases, as well as the mixed lineage kinase ZAK and to block the downstream cellular events mediated by these enzymes.
	Important information about its composition: Tasigna® is available as 50 mg, 150 mg and 200 mg nilotinib (active ingredient) hard gelatin capsules and contains lactose monohydrate, crospovidone type A, poloxamer 188, colloidal anhydrous silica, and magnesium stearate as excipients.
Hyperlink to the Product Information	[Proposed SmPC]
Indication(s) in the EEA	**Current:** • Treatment of adult and pediatric patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase (CP). • Treatment of adult patients with chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib. Efficacy data in patients with CML in blast crisis (BC) are not available. • Treatment of pediatric patients with chronic phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib.
	Proposed: Not Applicable

Dosage in the EEA	**Current:** **Posology for Philadelphia chromosome positive CML adult patients** The recommended dose is: - 300 mg twice daily in newly diagnosed patients with CML in the chronic phase, - 400 mg twice daily in patients with chronic or accelerated phase CML with resistance or intolerance to prior therapy. **Posology for Philadelphia chromosome positive CML pediatric patients** Dosing in pediatric patients is individualized and is based on body surface area (mg/m2). The recommended dose of nilotinib is 230 mg/m2 twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg). Different strengths of Tasigna hard capsules can be combined to attain the desired dose. There is no experience with treatment of pediatric patients below 2 years of age. There are no data in newly diagnosed pediatric patients below 10 years of age and limited data in imatinib-resistant or intolerant pediatric patients below 6 years of age. Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.
	Proposed: Not Applicable
Pharmaceutical form and strengths	**Current:** Hard capsules of 50 mg, 150 mg and 200 mg
	Proposed: Not Applicable
Is/will the product be subject to additional monitoring in the EU?	No

2 Part II Safety specification Module SI: Epidemiology of the indication(s) and target population

2.1 Indication: chronic myelogenous leukemia

Incidence:

Chronic myelogenous leukemia is the most common of the myeloproliferative neoplasm and it accounts for approximately 12% of all cases of leukemia (Siegel et al 2015). In Europe, based on data from the HAEMACARE project, the incidence of CML for the period 2000-2002 was 1.10 cases per 100,000 population [95% confidence intervals (CI): 1.06-1.15], with the highest age-standardized rates per 100,000 observed in southern countries (incidence rate 1.16) and the lowest in northern countries, and UK and Ireland (incidence rate 0.85) (Sant et al 2010). According to the EUTOS population-based registry that registered patients across 20 countries in Europe between 2008 and 2012, the age-standardized incidence of CML was 0.96 per 100,000 per year (Hoffmann et al 2015). In the United States, it was estimated that there would be 8990 new patients with CML in 2019 (SEER 2019).

Table 2-1 Estimated number of incident cases of EU in the year 2016

Countries	Incidence cases of CML		Source of data/ reference
	Male	Female	Both male and Female
France	584	360	944
Germany	767	662	1428
Italy	628	400	1029
Spain	398	230	628
United Kingdom	453	350	803
EU-28	3933	2645	6578

Source: GBD 2019

Prevalence:

There has been a growth in the prevalence of CML since the introduction of imatinib in 2001. In 2011, the number of people in the US, living with CML, had doubled since 2001 and this trend is expected to continue (Shah and Arceci 2012). In 2016, there were an estimated 54,226 people living with CML in the US (SEER 2019). According to RARECARENet (2008), the prevalence of CML in Europe was 32,412 persons in 2008. Data on prevalence of CML in the EU are limited. In a study in Sweden, the complete prevalence estimate for 2012 was 1.2 per 10,000 population (Gunnarsson et al 2016). In a German study, the estimated complete prevalence for 2012 was 1.1 per 10,000 population (1.2 and 1.1 per 10,000 population in males and females, respectively) in Germany (Lauseker et al 2016). In a study in the UK, the complete prevalence was 1.5 per 10,000 population (1.7 and 1.3 in males and females, respectively) (Li et al 2016).

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

The median age of diagnosis of CML was 65 years, according to SEER data from 2012 to 2016 (SEER 2019). Approximately 2.0% were diagnosed under the age of 20 years,

- 7.9% between 20 and 34 years
- 8.1% between 35 and 44 years
- 13.5% between 45 and 54 years
- 18.0% between 55 and 64 years
- 21.5% between 65 and 74 years
- 19.4% between 75 and 84 years
- 9.6% over 84 years of age.

Table 2-2 Incident rates by race and sex adjusted to the US population

Race/Ethnicity	Men (/100,000 men)	Women (/100,000 women)
All Races	2.4	1.4
White	2.5	1.5
Black	2.2	1.5
Asian/Pacific Islander	1.7	0.8
American Indian/Alaska Native	2.0	1.0
Hispanic	1.9	1.2

Source: SEER 2019

In a case control study in Minnesota (US) that compared 670 patients with myeloid leukemia (420 patients with acute myeloid leukemia and 186 patients with CML) and 701 population-based controls, a statistically significant association was observed between peptic ulcer and CML (OR 2.0; 95% CI: 1.1-3.8). A personal history of cancer also increased the risk for CML (OR 3.5; 95% CI: 2.0-5.8), which remained significant after adjusting for previous radiation or chemotherapy treatment (OR 3.6; 95% CI: 1.9-7.0) (Johnson et al 2012). Exposure to ionizing radiation has been reported as a risk factor. There is no known familial disposition to CML and it is unknown whether specific genetic variants predispose persons in the general population to develop CML. Rare germline mutations in *ABL1* cause an autosomal dominant syndrome characterized by congenital heart defects, skeletal malformations and a failure to thrive, although they have not been associated with a predisposition of leukaemia (Wang et al 2017). Some studies of families in which multiple members have developed myeloproliferative neoplasms including CML have suggested the presence of an autosomal dominant mutation that may predispose to acquisition of a secondary somatic mutation such as the Ph chromosome translocation or JAK2 mutation. A genome-wide association study of Korean and European cohorts suggested that persons with genetic variants at two chromosomal loci, 6q25.1 and 17p11.1, may be more likely to develop CML (Kim et al 2011).

The main existing treatment options:

When a patient has suspected CML prior to confirmation of the diagnosis, therapy with hydroxyurea may be used to reduce white blood cells counts close to normal levels. Treatment

is continued until the confirmation of Ph+ chromosome. When the diagnosis of CML is confirmed, the therapy with tyrosine kinase inhibitors (TKIs) starts (Cortes and Kantarjian 2012).

Between 2000 and 2005, patients were treated with imatinib at different doses (400 mg daily or 800 mg daily). One study compared the two doses of imatinib (TOPS trial) and showed no difference in the major molecular response (MMR) rate at 1 year, despite somewhat faster achievement of rates of MMR with the higher dose.

Since 2005, second generation TKIs (dasatinib, nilotinib, bosutinib, ponatinib) provided higher rates of early responses in CML treated patients compared with imatinib, with nearly 90% of patients achieving complete cytogenetic response by 3 months of therapy and also excellent event free survival and transformation-free survival (Cortes and Kantarjian 2012).

The combination of interferon-alpha with imatinib has been suggested as a possible treatment to improve the rate of MMR or superior molecular response (Preudhomme et al 2010, Simonsson et al 2011).

Patients most commonly start therapy with imatinib or with second generation TKIs as initial treatment although the safety profiles of the compounds differ and patient history should be considered.

The European Leukemia Network recommendations suggested the following treatment approach (Baccarani et al 2013, Baccarani et al 2015).

Table 2-3 Treatment approach by EU Leukemia Network recommendations

Chronic phase	
First line	
All patients	Imatinib 400 mg daily, nilotinib 300 mg bid, or dasatinib 100 mg daily.
	Human leukocyte antigen (HLA) type patients and siblings only in case of baseline warnings (high risk, major route clonal chromosomal abnormalities in Ph+ cells (CCA/Ph1)).
Second line, intolerance to the first TKI	
Anyone of the other TKIs approved first line (imatinib, nilotinib, dasatinib)	
Second line, failure of imatinib first line	Dasatinib or nilotinib or bosutinib or ponatinib.
	HLA type patients and siblings.
Second line, failure of nilotinib first line	Dasatinib or bosutinib or ponatinib.
	HLA type patients and siblings; search for an unrelated stem cell donor; consider allogeneic hematopoietic stem-cell transplantation (allo-SCT).
Second line, failure of dasatinib first line	Nilotinib or bosutinib or ponatinib
	HLA type patients and siblings; search for an unrelated stem cell donor; consider allo-SCT.
Third line, failure of and/or intolerance to 2 TKIs	
	Anyone of the remaining TKIs; allo-SCT recommended in all eligible patients.

Any line, T315I mutation	Ponatinib
	HLA type patients and siblings; search for an unrelated stem cell donor; consider allo-SCT.
Accelerated and blast phase (BP)	
AP and BP in newly diagnosed, TKI-naive patients	Imatinib 400 mg twice daily or dasatinib 70 mg twice daily or 140 mg once daily.
	Stem cell donor search. Then, allo-SCT is recommended for all BP patients and for the AP patients who do not achieve an optimal response.
	Chemotherapy may be required before allo-SCT, to control the disease.
AP and BP as a progression from CP in TKI-pretreated patients	Any of the TKIs that were not used before progression (ponatinib in case of T315I mutation), then allo-SCT in all patients.
	Chemotherapy is frequently required to make patients eligible for allo-SCT.

Also approved, for patients in whom prior TKI therapy fails, are radotinib, which is available in Korea, and omacetaxine, which is a non-TKI drug approved by the US Food and Drug Administration (FDA) (Baccarani et al 2013).

Natural history of the indicated condition in the population, including mortality and morbidity:

In the US from 2012-2016, the median age at death for CML was 77 years.

Approximately 0.5% died under age 20

- 2.8% between the ages of 20 and 34 years
- 3.6% between the ages of 35 and 44 years
- 6.9% between the ages of 45 and 54 years
- 11.6% between the ages of 55 and 64 years
- 18.2% between the ages of 65 and 74 years
- 30.0% between the ages of 75 and 84 years
- 26.4% over 84 years of age.

The age-adjusted death rate was 0.3 per 100,000 men and women per year (SEER 2019).

Table 2-4 Mortality and morbidity

Race/Ethnicity	Men (/100,000 men)	Women (/100,000 women)
All Races	0.4	0.2
White	0.4	0.2
Black	0.4	0.2
Asian/Pacific Islander	0.2	0.1
American Indian/Alaska Native	N/A	N/A
Hispanic	0.3	0.2

N/A: Statistic not displayed due to less than 16 cases; SEER 2019

Millot et al (2005) published the signs and symptoms at the time of diagnosis of 40 children and adolescents treated for CML in 16 French centers. The clinical features at diagnosis (in 430 patients) over a 16-year period is presented in Table 2-5.

Table 2-5 Symptoms at diagnosis of CML patients

Symptom (children-adolescent / all ages)	Children and adolescent (%)	All ages (%)
Asthenia / fatigue or lethargy	45	33.5
Abdominal fullness	7.5	14.8
Abdominal pain	5	-
Ankle oedema	-	2.2
Anorexia	2.5	-
Arthralgia	-	4.0
Bleeding	17.5	21.3
Bone pain	7.5	7.4
Chest pain/dyspnea	5	4.5
Cough	2.5	3.1
Dizziness	-	2.2
Fever/sweats	10	14.6
Headache	2.5	5.8
Hearing disturbance	2.5	0.2
Infection	-	6.2
Malaise	-	3.1
Mental change (somnolence, inability to concentrate, memory loss, depression)	-	1.6
Nausea/vomiting	2.5	2.2
Priapism	4	1.9
Splenic discomfort	20	18.6
Visual disturbances	2.5	4.4
Weakness	-	4.4
Weight loss	17.5	20.0

Source: Millot et al 2005, Savage et al 1997

Important co-morbidities:

A retrospective cohort study on 878 CML patients was performed in two US administrative claims databases from 1997 to 2011. The study intended to analyze clinical and economic outcomes and treatment adherence of nilotinib and dasatinib as second-line treatments in imatinib resistant or intolerant patients. Diseases were identified using reported International classification of diseases-9th revision-clinical modification (ICD-9-CM) codes in medical claims. This type of study has limitations since there may be some inaccuracies in coding diagnosis and procedures and they do not include patient's complete profile or relevant disease risk factors such as family history or disease severity. Table 2-6 summarizes the comorbidities of those patients before they started treatment with nilotinib or dasatinib (Guerin et al 2012).

Table 2-6 Comorbidities (%) in adult CML patients starting second-line therapy

Comorbidity	Nilotinib patients (n=328)	Dasatinib patients (n=550)	P Value
Anemia	72.0	65.5	0.046*
Chronic pulmonary disease	21.0	17.1	ns
Cardiovascular disease	22.6	17.8	ns
Cerebrovascular disease	8.5	9.5	ns
Congestive heart failure	5.2	4.9	ns
Coagulopathy	12.8	14.4	ns
Depression	17.4	10.9	0.006*
Diabetes	23.2	22.2	ns
Fibromyalgia	7.3	11.6	0.039*
Fluid electrolyte disorders	19.5	15.6	ns
Hyperlipidemia	43.0	34.0	0.008*
Hypertension	47.3	38.5	0.011*
Hypothyroidism	12.8	11.5	ns
Liver disease	5.5	5.8	ns
Lymphoma	11.0	10.2	ns
Macular degeneration	5.2	4.7	ns
Neurologic disorders	7.0	4.9	ns
Obesity	6.1	7.8	ns
Osteoporosis	8.5	5.3	ns
Peripheral vascular disease	13.4	6.4	<0.001*
Psychoses	9.5	6.4	ns
Renal failure	17.7	4.9	ns
Solid tumor	17.7	15.3	ns
Valvular disease	19.5	12.4	0.004*

*significant at the 5% level
ns: non-significant

Gugliotta et al (2013) reviewed studies reporting the effect of comorbidities in the treatment of CML with TKIs. Most of the retrieved studies used different co-morbidities indexes that did not allow to having separate information about those specific co-morbidities. However, a sub-

analysis of the DASISION study to assess the impact of baseline comorbidities on the safety and efficacy of first-line dasatinib and imatinib in Chronic Myeloid Leukemia in Chronic Phase (CML-CP) patients reported that 48% of patients on dasatinib and 46% on imatinib had two or more comorbidities. In order of frequency; gastrointestinal (33-35%), muscle-skeletal (27-31%), endocrine-metabolic (excluding diabetes 17-21%), cardiovascular (CV) (13-17%), respiratory (13-14%), dermatologic (12%), hepatobiliary (9-12%), hyperlipidemia (7-9%), diabetes mellitus (5-7%), and renal (5-7%).

3 Part II Safety specification Module SII: Non-clinical part of the safety specification

Table 3-1 Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
Safety Pharmacology No effects on central nervous system (CNS) or respiratory functions. In vitro cardiac safety studies demonstrated a preclinical signal for QT prolongation. No biologically relevant findings on contractility of coronary and subcutaneous resistance arteries as well as on platelet function and coagulation parameters.	There were no effects on CNS or respiratory functions in human beings. However, QT prolongation was observed in clinical trials.
Additional cardiac safety Electron microscopic examination of heart tissue from the 39-week monkey and the 13-week rat toxicity studies found no ultrastructural changes in both species. Data from in vitro studies showed that cytotoxic concentrations of nilotinib (≥ 10 µM) are required to trigger activation of the endoplasmic reticulum stress response, collapse of the mitochondrial membrane potential and cell death in Neonatal Rat Ventricular Myocytes (NRVM). Similar changes were also observed in heart fibroblasts (primary culture) in vitro indicating lack of specificity for cardiomyocytes. Data from the 4-week rat exploratory studies did reveal an increase of the heart weight, although without any histopathological or electron microscopic changes or effects on heart structure or function. The increase in relative left ventricular (LV) mass in rats administered nilotinib at 80 mg/kg/day was not supported by any structural changes as assessed by MRI. In addition, increases in LV end-diastolic wall thickness and end-diastolic volume observed in the vehicle group over the course of the study, which are indicative of normal growth, were not affected by nilotinib treatment. Although a small transient increase in LV stroke volume was seen in the nilotinib-treated rats, the LV ejection fraction, an index of contractile function, was similar among the vehicle and nilotinib treated groups at both 2 and 4 weeks. Therefore, it is unclear whether these small transient increases in stroke volume have any biological significance. In the rat in vivo studies, the nilotinib exposures (in terms of Cmax or AUC0-24h) achieved were comparable or higher than those reported for patients at 800 mg/day.	Hadzijusufovic et al (2011) reported that nilotinib exerts direct effects on vascular endothelial cells by inhibiting the growth of the human microvascular endothelial cell line HMEC-1 (IC50 0.5–1.5 µM) and, in a scratch-wound healing assay, by inhibiting human vascular endothelial cells (HUVEC) migration and sprouting. The authors concluded that it was unknown whether these drug effects contribute to vascular events seen in patients treated with nilotinib. Novartis have previously assessed the effect of nilotinib on the proliferation of HUVEC induced by VEGF, bFGF or on growth- (5% fetal calf serum (FCS)) or basal- (1.5% FCS) medium conditions (Report RD-2006-01362). At concentrations ≤1 µM nilotinib did not substantially affect the proliferation of HUVEC induced by VEGF, bFGF or on growth- (5% FCS) or basal- (1.5% FCS) medium conditions. At a concentration of 100 nM a slight, but significant enhancement of VEGF-induced proliferation was observed and at 1 µM a slight decrease in bFGF and FCS induced proliferation was seen. At a nilotinib concentration of 10 µM, the proliferation of HUVEC was reduced below baseline indicating cell loss, however, this concentration level of nilotinib tends to show general cytotoxicity.

Key Safety findings (from non-clinical studies)	Relevance to human usage
	In conclusion and in contrast to Hadzijusufovic et al (2011), this study showed no evidence for a substantial toxic effect of nilotinib on human vascular endothelial cells.
Hematologic changes Mild hematological changes were observed in mice (reduced red blood cell counts together with reductions in hemoglobin), rats (increases in total leukocyte counts, neutrophil counts, lymphocyte counts and monocyte counts, decreases of erythrocyte counts, hemoglobin concentrations, and hematocrit values) and monkeys (increases in platelet counts, decreases in red cell mass), prolongation in activated partial thromboplastin time at oral doses ≥ 20 mg/kg for mice and rats and 200 mg/kg for monkeys.	Hematological changes have been noticed in clinical development, as expected with any anti-leukemic drugs.
Liver toxicity Liver was the main target organ of toxicity in dogs and monkeys and to a minor degree in rats and mice. In dogs, clinical chemistry (increased alanine aminotransferase (ALT) and alkaline phosphatase activity and in females only, bilirubinuria and hyperbilirubinemia) and histopathology findings consistent with hepatobiliary toxicity were observed. Microscopic findings included sinusoidal aggregates of hyperplastic and/or hypertrophic Kupffer cells, occasionally accompanied by bile duct proliferation, centrilobular bile inspissations and leukocytic inflammation. In cynomolgus monkeys, hepatic lesions were characterized by bile duct hyperplasia, sinusoidal cell hyperplasia/hypertrophy, cytoplasmic aggregation of sinusoidal cells and periportal fibrosis. Increases in ALT as well as total cholesterol levels were also seen. In the mouse tolerability study centrilobular hepatocellular hypertrophy was present and in the mouse 4-week in feed study increases in total, direct and indirect bilirubin levels were noted, however without any associated histopathological changes. In the rat dose-range finding study, slight chronic inflammation together with minimal single cell necrosis of hepatocytes were observed at high dose. Doses used in the 4-week (gavage and in feed) and 26-week toxicity studies in rats were devoid of any histopathological liver changes. In general, the changes in clinical chemistry were mostly reversible after a four week recovery period, the histological alterations only showed partial reversibility.	Hepatotoxicity is a known adverse drug reaction (ADR) for nilotinib.
Renal toxicity Minor effects were seen in kidneys of mice and consisted of an increased incidence of renal tubular basophilia.	Not observed in clinical development.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Reproductive toxicity No effects on fertility parameters or reproductive performance were observed during the fertility study in rats. Embryo-fetal development studies did not indicate teratogenicity. Nilotinib was embryotoxic and fetotoxic in rabbits and rats at doses associated with maternal toxicity. In the pre- and post-natal study, administration of nilotinib to F0 female rats was associated with decreased pup body weight and changes in some physical development parameters at a dose that produced maternal effects. Nilotinib administered to juvenile animals via oral gavage at doses of 2, 6 and 20 mg/kg/day was well tolerated. Effects (reductions in body weight parameters and food consumption) were limited to the dose of 20 mg/kg/day and were reversible. The No-Observable-Effect-Level (NOEL) in juvenile rats was considered to be 6 mg/kg/day. Nilotinib is transferred into the milk in lactating rats with a milk/plasma concentration ratio of approximately 2.	Reproductive toxicity/pregnancy is an important potential risk in the RMP.
Genotoxicity No genotoxicity observed (in vitro or in vivo).	No genotoxicity was observed in clinical development.
Phototoxicity Phototoxic potential suggested in vitro, but no effects have been observed in vivo.	No phototoxicity was observed in clinical development.
Carcinogenicity There was no evidence of carcinogenicity in the 2-year rat carcinogenicity study upon administration of nilotinib at 5, 15 and 40 mg/kg/day. Exposures at the highest dose level represented approximately 2x to 3x human daily steady state exposure (based on area under the curve (AUC) to nilotinib at the dose of 800 mg/day. The major target organ for non-neoplastic lesions was the uterus (dilatation, vascular ectasia, hyperplasia endothelial cell, inflammation and/or epithelial hyperplasia). In the 26-week Tg.rasH2 mouse carcinogenicity study where nilotinib was administered at 30, 100 and 300 mg/kg/day, skin papilloma/carcinoma were detected at 300 mg/kg representing approximately 30 to 40 times (based on AUC) the human exposure at the maximum approved dose 800mg/day (administered as 400 mg twice a day). The NOEL for the skin neoplastic lesions was 100 mg/kg/day, representing approximately 10 to 20 times the human exposure at the maximum approved dose 800 mg/day (administered as 400 mg twice a day). The major target organs for non-neoplastic lesions were the skin (epidermal hyperplasia), the growing teeth (degeneration/atrophy of the enamel organ of upper incisors and inflammation of the gingiva/odontogenic epithelium of incisors) and the thymus (increased incidence and/or severity of decreased lymphocytes).	Skin malignancy is an important potential risk in the RMP.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Mechanisms for drug interactions	
Nilotinib was shown to inhibit the activity of cytochrome P450 (CYP) isoenzymes (CYP2C8 (Ki=0.24 µM), CYP2C9 (Ki=0.13 µM), CYP2D6 (Ki=1.5 µM), CYP3A4/5 (Ki=0.45 µM)), and Uridine 5' Diphospho-Glucuronosyltransferase (UGT1A1) (Ki=0.19 µM), as well as drug transporters (organic anion-transporting polypeptides (OATP1B1) (IC50=1.10 µM), OATP1B3 (IC50=5.62 µM), organic cation transporter (OCT1) (IC50=1.0 µM), and P-glycoprotein (P-gp) (IC50=1.7 µM)) in the in vitro systems. Nilotinib was shown to be an inducer of CYP3A4, CYP2C8, and CYP2C9 activities in the in vitro study. CYP3A4 was shown to be the main contributor to the oxidative metabolism of nilotinib in the in vitro study.	These interactions have been identified in the clinical development as well.
Glucose changes	
No glucose changes were detected in the non-clinical toxicity studies.	Increase in blood glucose has been observed in clinical trials.
Cholesterol changes	
Increased levels of total cholesterol were seen in rat, dog and monkey toxicity studies	Increase in blood cholesterol has been observed in clinical trials also.
Other toxicity-related information or data	
None	None

4 Part II Safety specification Module SIII Clinical trial exposure

4.1 Part II Module SIII Clinical trial exposure

Table 4-1 Duration of exposure

	CAMN107A2101E1 and E2		CAMN107A2303		CAMN107A2109 (ENACT Study)		CAMN107A2203 and CAMN107A2120 (Pediatric population)		
	LPLV		LPLV		LPLV		LPLV		
	Imatinib-resistant/intolerant		Newly diagnosed		Imatinib-resistant/ intolerant		Imatinib/ dasatinib resistant/into lerant	Newly diagnosed	All patients
	CML-AP	CML-CP	CML-CP		CML-AP	CML-CP	Ph+ CML-CP		
	400 mg bid		300 mg bid	400 mg bid	400 mg bid		230 mg/m^2 bid		
Duration of exposure (months)	N=137 n (%)	N=321 n (%)	N=279 n (%)	N=277 n (%)	N=181 n (%)	N=1422 n (%)	N=44 n (%)	N=25 n (%)	N=69 n (%)
Mean (SD)	15.67 (18.54)	30.06 (27.51)	76.63 (46.35)	78.13 (45.31)	7.41 (6.38)	9.54 (6.45)	34.66 (25.15)	39.70 (22.66)	36.48 (24.23)
Median	8.67	18.43	82.79	87.49	5.26	8.74	31.80	51.91	39.62
Range (min-max)	0.1-75.7	0.0-77.7	0.1-135.4	0.2-134.8	0.2-24.2	0.0-26.5	0.7-63.5	1.4-61.2	0.7-63.5
< 3 months	25 (18.2)	52 (16.2)	13 (4.7)	16 (5.8)	57 (31.5)	266 (18.7)	2 (4.5)	1 (4.0)	3 (4.3)
≥ 3 - < 6 months	32 (23.4)	25 (7.8)	10 (3.6)	14 (5.1)	42 (23.2)	262 (18.4)	4 (9.1)	1 (4.0)	5 (7.2)
≥ 6 - < 12 months	24 (17.5)	46 (14.3)	13 (4.7)	9 (3.2)	37 (20.4)	390 (27.4)	10 (22.7)	2 (8.0)	12 (17.4)
≥ 12 - < 18 months	17 (12.4)	37 (11.5)	16 (5.7)	9 (3.2)	30 (16.6)	317 (22.3)	3 (6.8)	3 (12.0)	6 (8.7)
≥ 18 - < 24 months	13 (9.5)	26 (8.1)	13 (4.7)	8 (2.9)	14 (7.7)	172 (12.1)	2 (4.5)	1 (4.0)	3 (4.3)
≥ 24 - < 30 months	5 (3.6)	13 (4.0)	7 (2.5)	7 (2.5)	1 (0.6)	15 (1.1)	0	1 (4.0)	1 (1.4)
≥ 30 - < 36 months	3 (2.2)	13 (4.0)	5 (1.8)	4 (1.4)	0	0	2 (4.5)	2 (8.0)	4 (5.8)
≥ 36 - < 42 months	5 (3.6)	5 (1.6)	7 (2.5)	8 (2.9)	0	0	1 (2.3)	1 (4.0)	2 (2.9)
≥ 42 - < 48 months	2 (1.5)	5 (1.6)	6 (2.2)	5 (1.8)	0	0	-	-	-
≥ 48 - < 54 months	0	3 (0.9)	1 (0.4)	5 (1.8)	0	0	1 (2.3)	1 (4.0)	2 (2.9)

	CAMN107A2101E1 and E2		CAMN107A2303		CAMN107A2109 (ENACT Study)		CAMN107A2203 and CAMN107A2120 (Pediatric population)		
	LPLV		LPLV		LPLV		LPLV		
	Imatinib-resistant/intolerant		Newly diagnosed		Imatinib-resistant/ intolerant		Imatinib/ dasatinib resistant/into lerant	Newly diagnosed	All patients
	CML-AP	CML-CP	CML-CP		CML-AP	CML-CP	Ph+ CML-CP		
	400 mg bid		300 mg bid	400 mg bid	400 mg bid		230 mg/m^2 bid		
Duration of exposure (months)	N=137 n (%)	N=321 n (%)	N=279 n (%)	N=277 n (%)	N=181 n (%)	N=1422 n (%)	N=44 n (%)	N=25 n (%)	N=69 n (%)
≥ 54 - < 60 months	1 (0.7)	11 (3.4)	17 (6.1)	10 (3.6)	0	0	0	2 (8.0)	2 (2.9)
≥ 60 - < 66 months	-	-	-	-	0	0	19 (43.2)	10 (40.0)	29 (42.0)
≥ 60 - < 72 months	7 (5.1)	59 (18.4)	21 (7.5)	25 (9.0)	0	0	-	-	-
≥ 72 - < 84 months	3 (2.2)	26 (8.1)	12 (4.3)	14 (5.1)	0	0	-	-	-
≥ 84 - < 96 months	0	0	7 (2.5)	18 (6.5)	0	0	-	-	-
≥ 96 - < 108 months	0	0	15 (5.4)	8 (2.9)	0	0	-	-	-
≥ 108 - < 120 months	0	0	15 (5.4)	30 (10.8)	0	0	-	-	-
≥ 120 - < 132 months	0	0	100 (35.8)	85 (30.7)	0	0	-	-	-
≥ 132 - < 144 months	0	0	1 (0.4)	2 (0.7)	0	0	-	-	-
Cumulative exposure									
≥ 3 months	112 (81.8)	269 (83.8)	266 (95.3)	261 (94.2)	124 (68.5)	1156 (81.3)	42 (95.5)	24 (96.0)	66 (95.7)
≥ 6 months	80 (58.4)	244 (76.0)	256 (91.8)	247 (89.2)	82 (45.3)	894 (62.9)	38 (86.4)	23 (92.0)	61 (88.4)
≥ 12 months	56 (40.9)	198 (61.7)	243 (87.1)	238 (85.9)	45 (24.9)	504 (35.4)	28 (63.6)	21 (84.0)	49 (71.0)
≥ 18 months	39 (28.5)	161 (50.2)	227 (81.4)	229 (82.7)	15 (8.3)	187 (13.2)	25 (56.8)	18 (72.0)	43 (62.3)
≥ 24 months	26 (19.0)	135 (42.1)	214 (76.7)	221 (79.8)	1 (0.6)	15 (1.1)	23 (52.3)	17 (68.0)	40 (58.0)
≥ 30 months	21 (15.3)	122 (38.0)	207 (74.2)	214 (77.3)	0	0	23 (52.3)	16 (64.0)	39 (56.5)
≥ 36 months	18 (13.1)	109 (34.0)	202 (72.4)	210 (75.8)	0	0	21 (47.7)	14 (56.0)	35 (50.7)

	CAMN107A2101E1 and E2		CAMN107A2303		CAMN107A2109 (ENACT Study)		CAMN107A2203 and CAMN107A2120 (Pediatric population)		
	LPLV		LPLV		LPLV		LPLV		
	Imatinib-resistant/intolerant		Newly diagnosed		Imatinib-resistant/ intolerant		Imatinib/ dasatinib resistant/into lerant	Newly diagnosed	All patients
	CML-AP	CML-CP	CML-CP		CML-AP	CML-CP	Ph+ CML-CP		
Duration of exposure (months)	400 mg bid		300 mg bid	400 mg bid	400 mg bid		230 mg/m^2 bid		
	N=137 n (%)	N=321 n (%)	N=279 n (%)	N=277 n (%)	N=181 n (%)	N=1422 n (%)	N=44 n (%)	N=25 n (%)	N=69 n (%)
≥ 42 months	13 (9.5)	104 (32.4)	195 (69.9)	202 (72.9)	0	0	20 (45.5)	13 (52.0)	33 (47.8)
≥ 48 months	11 (8.0)	99 (30.8)	189 (67.7)	197 (71.1)	0	0	20 (45.5)	13 (52.0)	33 (47.8)
≥ 54 months	11 (8.0)	96 (29.9)	188 (67.4)	192 (69.3)	0	0	19 (43.2)	12 (48.0)	31 (44.9)
≥ 60 months	10 (7.3)	85 (26.5)	171 (61.3)	182 (65.7)	0	0	19 (43.2)	10 (40.0)	29 (42.0)
≥ 72 months	3 (2.2)	26 (8.1)	150 (53.8)	157 (56.7)	0	0	-	-	-
≥ 84 months	0	0	138 (49.5)	143 (51.6)	0	0	-	-	-
≥ 96 months	0	0	131 (47.0)	125 (45.1)	0	0	-	-	-
≥ 108 months	0	0	116 (41.6)	117 (42.2)	0	0	-	-	-
≥ 120 months	0	0	101 (36.2)	87 (31.4)	0	0	-	-	-
≥ 132 months	0	0	1 (0.4)	2 (0.7)	0	0	-	-	-
Total patient-months	2146.79	9649.26	21379.77	21642.01	1340.55	13566.95	1525.00	992.50	2517.50

- Exposure (months) = (last date of study drug - start date of study drug +1)/30.4375 (ie interruption periods are also included in the calculation of exposure)
- Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (months).
- One patient in the CML-AP group with missing imatinib-resistance/intolerance criteria at baseline was included in the analysis.

Source: [Annex 7-Table 12-1], [Annex 7-Table 12-5], [Annex 7-Table 1.2-1p].

Table 4-2 Exposure by age group

	CAMN107A2101E1 and E2				CAMN107A2303				CAMN107A2109 (ENACT Study)				CAMN107A2203 and CAMN107A2120 (Pediatric population)					
	LPLV				LPLV				LPLV				LPLV					
	Imatinib-resistant/intolerant				Newly diagnosed				Imatinib-resistant/ intolerant				Imatinib/ dasatinib resistant/ intolerant		Newly diagnosed		All patients	
	CML-AP		CML-CP		CML-CP				CML-AP		CML-CP		Ph+ CML-CP					
	400 mg bid				300 mg bid		400 mg bid		400 mg bid				230 mg/m^2 bid					
Duration of exposure (months)	<65 yr N=96 n (%)	≥ 65 yr N=41 n (%)	<65 yr N=223 n (%)	≥ 65 yr N=98 n (%)	<65 yr N=244 n (%)	≥ 65 yr N=35 n (%)	<65 yr N=253 n (%)	≥ 65 yr N=24 n (%)	<65 yr N=149 n (%)	≥ 65 yr N=32 n (%)	<65 yr N=1128 n (%)	≥ 65 yr N=294 n (%)	2 to < 12 yr N=18 n (%)	12 to < 18 yr N=26 n (%)	2 to < 12 yr N=6 n (%)	12 to < 18 yr N=19 n (%)	2 to < 12 yr N=24 n (%)	12 to < 18 yr N=45 n (%)
Mean	16.55	13.60	31.45	26.88	78.25	65.37	81.45	43.18	7.48	7.07	9.65	9.12	32.30	36.29	40.87	39.33	34.44	37.57
SD	20.06	14.34	28.22	25.67	46.87	41.43	44.52	39.01	6.32	6.73	6.34	6.84	25.89	25.00	20.51	23.82	24.52	24.28
Median	9.03	8.31	19.68	15.52	89.31	62.09	93.83	35.83	5.65	3.73	8.84	7.52	15.16	36.55	45.62	51.91	31.72	40.87
Range (min-max)	0.1-75.7	0.1-64.9	0.1-77.7	0.0-76.7	0.1-135.4	0.4-127.6	0.2-134.8	0.2-127.7	0.2-24.2	0.3-21.6	0.0-26.5	0.0-26.2	2.4-63.5	0.7-62.5	8.7-61.2	1.4-61.2	2.4-63.5	0.7-62.5
< 3 months	17 (17.7)	8 (19.5)	34 (15.2)	18 (18.4)	11 (4.5)	2 (5.7)	10 (4.0)	6 (25.0)	45 (30.2)	12 (37.5)	196 (17.4)	70 (23.8)	1 (5.6)	1 (3.8)	0	1 (5.3)	1 (4.2)	2 (4.4)
≥ 3 - < 6 months	23 (24.0)	9 (22.0)	20 (9.0)	5 (5.1)	10 (4.1)	0	14 (5.5)	0	35 (23.5)	7 (21.9)	205 (18.2)	57 (19.4)	1 (5.6)	3 (11.5)	0	1 (5.3)	1 (4.2)	4 (8.9)

	CAMN107A2101E1 and E2				CAMN107A2303				CAMN107A2109 (ENACT Study)				CAMN107A2203 and CAMN107A2120 (Pediatric population)					
	LPLV				LPLV				LPLV				LPLV					
	Imatinib-resistant/intolerant				Newly diagnosed				Imatinib-resistant/ intolerant				Imatinib/ dasatinib resistant/ intolerant		Newly diagnosed		All patients	
	CML-AP		CML-CP		CML-CP				CML-AP		CML-CP		Ph+ CML-CP					
	400 mg bid				300 mg bid		400 mg bid		400 mg bid				230 mg/m^2 bid					
Duration of exposure (months)	<65 yr N=96 n (%)	≥ 65 yr N=41 n (%)	<65 yr N=223 n (%)	≥ 65 yr N=98 n (%)	<65 yr N=244 n (%)	≥ 65 yr N=35 n (%)	<65 yr N=253 n (%)	≥ 65 yr N=24 n (%)	<65 yr N=149 n (%)	≥ 65 yr N=32 n (%)	<65 yr N=1128 n (%)	≥ 65 yr N=294 n (%)	2 to < 12 yr N=18 n (%)	12 to < 18 yr N=26 n (%)	2 to < 12 yr N=6 n (%)	12 to < 18 yr N=19 n (%)	2 to < 12 yr N=24 n (%)	12 to < 18 yr N=45 n (%)
≥ 6 - < 12 months	18 (18.8)	6 (14.6)	25 (11.2)	21 (21.4)	11 (4.5)	2 (5.7)	8 (3.2)	1 (4.2)	33 (22.1)	4 (12.5)	322 (28.5)	68 (23.1)	6 (33.3)	4 (15.4)	1 (16.7)	1 (5.3)	7 (29.2)	5 (11.1)
≥ 12 - < 18 months	11 (11.5)	6 (14.6)	29 (13.0)	8 (8.2)	12 (4.9)	4 (11.4)	8 (3.2)	1 (4.2)	23 (15.4)	7 (21.9)	260 (23.0)	57 (19.4)	2 (11.1)	1 (3.8)	0	3 (15.8)	2 (8.3)	4 (8.9)
≥ 18 - < 24 months	9 (9.4)	4 (9.8)	21 (9.4)	5 (5.1)	13 (5.3)	0	6 (2.4)	2 (8.3)	12 (8.1)	2 (6.3)	135 (12.0)	37 (12.6)	0	2 (7.7)	0	1 (5.3)	0	3 (6.7)
≥ 24 - < 30 months	2 (2.1)	3 (7.3)	8 (3.6)	5 (5.1)	5 (2.0)	2 (5.7)	6 (2.4)	1 (4.2)	1 (0.7)	0	10 (0.9)	5 (1.7)	0	0	1 (16.7)	0	1 (4.2)	0
≥ 30 - < 36 months	1 (1.0)	2 (4.9)	6 (2.7)	7 (7.1)	5 (2.0)	0	3 (1.2)	1 (4.2)	0	0	0	0	0	2 (7.7)	1 (16.7)	1 (5.3)	1 (4.2)	3 (6.7)
≥ 36 - < 42 months	4 (4.2)	1 (2.4)	4 (1.8)	1 (1.0)	7 (2.9)	0	7 (2.8)	1 (4.2)	0	0	0	0	0	1 (3.8)	0	1 (5.3)	0	2 (4.4)

	CAMN107A2101E1 and E2				CAMN107A2303				CAMN107A2109 (ENACT Study)				CAMN107A2203 and CAMN107A2120 (Pediatric population)					
	LPLV				LPLV				LPLV				LPLV					
	Imatinib-resistant/intolerant				Newly diagnosed				Imatinib-resistant/ intolerant				Imatinib/ dasatinib resistant/ intolerant		Newly diagnosed		All patients	
	CML-AP		CML-CP		CML-CP				CML-AP		CML-CP		Ph+ CML-CP					
	400 mg bid				300 mg bid		400 mg bid		400 mg bid				230 mg/m^2 bid					
Duration of exposure (months)	<65 yr	≥ 65 yr	<65 yr	≥ 65 yr	<65 yr	≥ 65 yr	<65 yr	≥ 65 yr	<65 yr	≥ 65 yr	<65 yr	≥ 65 yr	2 to < 12 yr	12 to < 18 yr	2 to < 12 yr	12 to < 18 yr	2 to < 12 yr	12 to < 18 yr
	N=96 n (%)	N=41 n (%)	N=223 n (%)	N=98 n (%)	N=244 n (%)	N=35 n (%)	N=253 n (%)	N=24 n (%)	N=149 n (%)	N=32 n (%)	N=1128 n (%)	N=294 n (%)	N=18 n (%)	N=26 n (%)	N=6 n (%)	N=19 n (%)	N=24 n (%)	N=45 n (%)
≥ 42 - < 48 months	1 (1.0)	1 (2.4)	0	5 (5.1)	3 (1.2)	3 (8.6)	4 (1.6)	1 (4.2)	0	0	0	0	-	-	-	-	-	-
≥ 48 - < 54 months	0	0	2 (0.9)	1 (1.0)	1 (0.4)	0	5 (2.0)	0	0	0	0	0	1 (5.6)	0	0	1 (5.3)	1 (4.2)	1 (2.2)
≥ 54 - < 60 months	1 (1.0)	0	7 (3.1)	4 (4.1)	13 (5.3)	4 (11.4)	7 (2.8)	3 (12.5)	0	0	0	0	0	0	2 (33.3)	0	2 (8.3)	0
≥ 60 - < 66 months	-	-	-	-	-	-	-	-	0	0	0	0	7 (38.9)	12 (46.2)	1 (16.7)	9 (47.4)	8 (33.3)	21 (46.7)
≥ 60 - < 72 months	6 (6.3)	1 (2.4)	46 (20.6)	13 (13.3)	17 (7.0)	4 (11.4)	23 (9.1)	2 (8.3)	0	0	0	0	-	-	-	-	-	-
≥ 72 - < 84 months	3 (3.1)	0	21 (9.4)	5 (5.1)	10 (4.1)	2 (5.7)	13 (5.1)	1 (4.2)	0	0	0	0	-	-	-	-	-	-

	CAMN107A2101E1 and E2				CAMN107A2303				CAMN107A2109 (ENACT Study)				CAMN107A2203 and CAMN107A2120 (Pediatric population)					
	LPLV				LPLV				LPLV				LPLV					
	Imatinib-resistant/intolerant				Newly diagnosed				Imatinib-resistant/ intolerant				Imatinib/ dasatinib resistant/ intolerant		Newly diagnosed		All patients	
	CML-AP		CML-CP		CML-CP				CML-AP		CML-CP		Ph+ CML-CP					
	400 mg bid				300 mg bid		400 mg bid		400 mg bid				230 mg/m^2 bid					
Duration of exposure (months)	**<65 yr**	**≥ 65 yr**	**<65 yr**	**≥ 65 yr**	**<65 yr**	**≥ 65 yr**	**<65 yr**	**≥ 65 yr**	**<65 yr**	**≥ 65 yr**	**<65 yr**	**≥ 65 yr**	**2 to < 12 yr**	**12 to < 18 yr**	**2 to < 12 yr**	**12 to < 18 yr**	**2 to < 12 yr**	**12 to < 18 yr**
	N=96 n (%)	**N=41 n (%)**	**N=223 n (%)**	**N=98 n (%)**	**N=244 n (%)**	**N=35 n (%)**	**N=253 n (%)**	**N=24 n (%)**	**N=149 n (%)**	**N=32 n (%)**	**N=1128 n (%)**	**N=294 n (%)**	**N=18 n (%)**	**N=26 n (%)**	**N=6 n (%)**	**N=19 n (%)**	**N=24 n (%)**	**N=45 n (%)**
≥ 84 - < 96 months	0	0	0	0	6 (2.5)	1 (2.9)	16 (6.3)	2 (8.3)	0	0	0	0	-	-	-	-	-	-
≥ 96 - < 108 months	0	0	0	0	12 (4.9)	3 (8.6)	8 (3.2)	0	0	0	0	0	-	-	-	-	-	-
≥ 108 - < 120 months	0	0	0	0	11 (4.5)	4 (11.4)	30 (11.9)	0	0	0	0	0	-	-	-	-	-	-
≥ 120 - < 132 months	0	0	0	0	96 (39.3)	4 (11.4)	83 (32.8)	2 (8.3)	0	0	0	0	-	-	-	-	-	-
≥ 132 - < 144 months	0	0	0	0	1 (0.4)	0	2 (0.8)	0	0	0	0	0	-	-	-	-	-	-

Cumulative exposure

	CAMN107A2101E1 and E2				CAMN107A2303				CAMN107A2109 (ENACT Study)				CAMN107A2203 and CAMN107A2120 (Pediatric population)					
	LPLV				LPLV				LPLV				LPLV					
	Imatinib-resistant/intolerant				Newly diagnosed				Imatinib-resistant/ intolerant				Imatinib/ dasatinib resistant/ intolerant		Newly diagnosed		All patients	
	CML-AP		CML-CP		CML-CP				CML-AP		CML-CP		Ph+ CML-CP					
	400 mg bid				300 mg bid		400 mg bid		400 mg bid				230 mg/m^2 bid					
Duration of exposure (months)	<65 yr	≥ 65 yr	<65 yr	≥ 65 yr	<65 yr	≥ 65 yr	<65 yr	≥ 65 yr	<65 yr	≥ 65 yr	<65 yr	≥ 65 yr	2 to < 12 yr	12 to < 18 yr	2 to < 12 yr	12 to < 18 yr	2 to < 12 yr	12 to < 18 yr
	N=96 n (%)	N=41 n (%)	N=223 n (%)	N=98 n (%)	N=244 n (%)	N=35 n (%)	N=253 n (%)	N=24 n (%)	N=149 n (%)	N=32 n (%)	N=1128 n (%)	N=294 n (%)	N=18 n (%)	N=26 n (%)	N=6 n (%)	N=19 n (%)	N=24 n (%)	N=45 n (%)
≥ 3 months	79 (82.3)	33 (80.5)	189 (84.8)	80 (81.6)	233 (95.5)	33 (94.3)	243 (96.0)	18 (75.0)	104 (69.8)	20 (62.5)	932 (82.6)	224 (76.2)	17 (94.4)	25 (96.2)	6 (100)	18 (94.7)	23 (95.8)	43 (95.6)
≥ 6 months	56 (58.3)	24 (58.5)	169 (75.8)	75 (76.5)	223 (91.4)	33 (94.3)	229 (90.5)	18 (75.0)	69 (46.3)	13 (40.6)	727 (64.5)	167 (56.8)	16 (88.9)	22 (84.6)	6 (100)	17 (89.5)	22 (91.7)	39 (86.7)
≥ 12 months	38 (39.6)	18 (43.9)	144 (64.6)	54 (55.1)	212 (86.9)	31 (88.6)	221 (87.4)	17 (70.8)	36 (24.2)	9 (28.1)	405 (35.9)	99 (33.7)	10 (55.6)	18 (69.2)	5 (83.3)	16 (84.2)	15 (62.5)	34 (75.6)
≥ 18 months	27 (28.1)	12 (29.3)	115 (51.6)	46 (46.9)	200 (82.0)	27 (77.1)	213 (84.2)	16 (66.7)	13 (8.7)	2 (6.3)	145 (12.9)	42 (14.3)	8 (44.4)	17 (65.4)	5 (83.3)	13 (68.4)	13 (54.2)	30 (66.7)
≥ 24 months	18 (18.8)	8 (19.5)	94 (42.2)	41 (41.8)	187 (76.6)	27 (77.1)	207 (81.8)	14 (58.3)	1 (0.7)	0	10 (0.9)	5 (1.7)	8 (44.4)	15 (57.7)	5 (83.3)	12 (63.2)	13 (54.2)	27 (60.0)
≥ 30 months	16 (16.7)	5 (12.2)	86 (38.6)	36 (36.7)	182 (74.6)	25 (71.4)	201 (79.4)	13 (54.2)	0	0	0	0	8 (44.4)	15 (57.7)	4 (66.7)	12 (63.2)	12 (50.0)	27 (60.0)

	CAMN107A2101E1 and E2				CAMN107A2303				CAMN107A2109 (ENACT Study)				CAMN107A2203 and CAMN107A2120 (Pediatric population)					
	LPLV				LPLV				LPLV				LPLV					
	Imatinib-resistant/intolerant				Newly diagnosed				Imatinib-resistant/ intolerant				Imatinib/ dasatinib resistant/ intolerant		Newly diagnosed		All patients	
	CML-AP		CML-CP		CML-CP				CML-AP		CML-CP		Ph+ CML-CP					
	400 mg bid				300 mg bid		400 mg bid		400 mg bid				230 mg/m^2 bid					
Duration of exposure (months)	<65 yr N=96 n (%)	≥ 65 yr N=41 n (%)	<65 yr N=223 n (%)	≥ 65 yr N=98 n (%)	<65 yr N=244 n (%)	≥ 65 yr N=35 n (%)	<65 yr N=253 n (%)	≥ 65 yr N=24 n (%)	<65 yr N=149 n (%)	≥ 65 yr N=32 n (%)	<65 yr N=1128 n (%)	≥ 65 yr N=294 n (%)	2 to < 12 yr N=18 n (%)	12 to < 18 yr N=26 n (%)	2 to < 12 yr N=6 n (%)	12 to < 18 yr N=19 n (%)	2 to < 12 yr N=24 n (%)	12 to < 18 yr N=45 n (%)
≥ 36 months	15 (15.6)	3 (7.3)	80 (35.9)	29 (29.6)	177 (72.5)	25 (71.4)	198 (78.3)	12 (50.0)	0	0	0	0	8 (44.4)	13 (50.0)	3 (50.0)	11 (57.9)	11 (45.8)	24 (53.3)
≥ 42 months	11 (11.5)	2 (4.9)	76 (34.1)	28 (28.6)	170 (69.7)	25 (71.4)	191 (75.5)	11 (45.8)	0	0	0	0	8 (44.4)	12 (46.2)	3 (50.0)	10 (52.6)	11 (45.8)	22 (48.9)
≥ 48 months	10 (10.4)	1 (2.4)	76 (34.1)	23 (23.5)	167 (68.4)	22 (62.9)	187 (73.9)	10 (41.7)	0	0	0	0	8 (44.4)	12 (46.2)	3 (50.0)	10 (52.6)	11 (45.8)	22 (48.9)
≥ 54 months	10 (10.4)	1 (2.4)	74 (33.2)	22 (22.4)	166 (68.0)	22 (62.9)	182 (71.9)	10 (41.7)	0	0	0	0	7 (38.9)	12 (46.2)	3 (50.0)	9 (47.4)	10 (41.7)	21 (46.7)
≥ 60 months	9 (9.4)	1 (2.4)	67 (30.0)	18 (18.4)	153 (62.7)	18 (51.4)	175 (69.2)	7 (29.2)	0	0	0	0	7 (38.9)	12 (46.2)	1 (16.7)	9 (47.4)	8 (33.3)	21 (46.7)
≥ 72 months	3 (3.1)	0	21 (9.4)	5 (5.1)	136 (55.7)	14 (40.0)	152 (60.1)	5 (20.8)	0	0	0	0	-	-	-	-	-	-

	CAMN107A2101E1 and E2				CAMN107A2303				CAMN107A2109 (ENACT Study)				CAMN107A2203 and CAMN107A2120 (Pediatric population)					
	LPLV				LPLV				LPLV				LPLV					
	Imatinib-resistant/intolerant				Newly diagnosed				Imatinib-resistant/ intolerant				Imatinib/ dasatinib resistant/ intolerant		Newly diagnosed		All patients	
	CML-AP		CML-CP		CML-CP				CML-AP		CML-CP		Ph+ CML-CP					
	400 mg bid				300 mg bid		400 mg bid		400 mg bid				230 mg/m^2 bid					
Duration of exposure (months)	<65 yr	≥ 65 yr	<65 yr	≥ 65 yr	<65 yr	≥ 65 yr	<65 yr	≥ 65 yr	<65 yr	≥ 65 yr	<65 yr	≥ 65 yr	2 to < 12 yr	12 to < 18 yr	2 to < 12 yr	12 to < 18 yr	2 to < 12 yr	12 to < 18 yr
	N=96 n (%)	N=41 n (%)	N=223 n (%)	N=98 n (%)	N=244 n (%)	N=35 n (%)	N=253 n (%)	N=24 n (%)	N=149 n (%)	N=32 n (%)	N=1128 n (%)	N=294 n (%)	N=18 n (%)	N=26 n (%)	N=6 n (%)	N=19 n (%)	N=24 n (%)	N=45 n (%)
≥ 84 months	0	0	0	0	126 (51.6)	12 (34.3)	139 (54.9)	4 (16.7)	0	0	0	0	-	-	-	-	-	-
≥ 96 months	0	0	0	0	120 (49.2)	11 (31.4)	123 (48.6)	2 (8.3)	0	0	0	0	-	-	-	-	-	-
≥ 108 months	0	0	0	0	108 (44.3)	8 (22.9)	115 (45.5)	2 (8.3)	0	0	0	0	-	-	-	-	-	-
≥ 120 months	0	0	0	0	97 (39.8)	4 (11.4)	85 (33.6)	2 (8.3)	0	0	0	0	-	-	-	-	-	-
≥ 132 months	0	0	0	0	1 (0.4)	0	2 (0.8)	0	0	0	0	0	-	-	-	-	-	-
Total patient-months	1588.80	557.60	7013.35	2634.24	19093.00	2287.95	20606.85	1036.32	1114.38	226.17	10885.75	2681.20	581.50	943.50	245.20	747.30	826.60	1690.80

- Exposure (months) = (last date of study drug - start date of study drug +1)/30.4375 (i.e. interruption periods are also included in the calculation of exposure)
- Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (months).
- One patient in the CML-AP group with missing imatinib-resistance/intolerance criteria at baseline was included in the analysis.

Source: [Annex 7–Table 12-2], [Annex 7-Table 1.2-2p] and [Annex 7-Table 12-6].

Table 4-3 Exposure by gender (Studies CAMN107A2101E1 and E2, CAMN107A2303, CAMN107A2203 and CAMN107A2120)

Duration of exposure (months)	CAMN107A2101E1 and E2				CAMN107A2303				CAMN107A2203 and CAMN107A2120 (Pediatric population)					
	LPLV				LPLV				LPLV					
	Imatinib-resistant/intolerant				Newly diagnosed				Imatinib/ dasatinib resistant/intolerant		Newly diagnosed		All patients	
	CML-AP		CML-CP		CML-CP				Ph+ CML-CP					
	400 mg bid				300 mg bid		400 mg bid		230 mg/m^2 bid					
	Male	Female	Male	Female	Male	Female	Male	Female	Male 2 to < 12 yr	Female 12 to < 18 yr	Male 2 to < 12 yr	Female 12 to < 18 yr	Male 2 to < 12 yr	Female 12 to < 18 yr
	N=76 n (%)	N=61 n (%)	N=162 n (%)	N=159 n (%)	N=156 n (%)	N=123 n (%)	N=173 n (%)	N=104 n (%)	N=27 n (%)	N=17 n (%)	N=13 n (%)	N=12 n (%)	N=40 n (%)	N=29 n (%)
Mean	15.23	16.21	30.07	30.05	74.98	78.72	78.09	78.21	34.8	34.4	45.7	33.2	38.4	33.9
SD	17.77	19.58	27.85	27.24	48.72	43.28	45.54	45.14	24.6	26.8	18.2	25.9	23.1	25.9
Median	9.17	8.31	17.22	20.67	86.19	81.48	87.49	87.67	31.4	32.2	55.4	28.1	46.4	32.2
Range	0.1-72.2	0.1-75.7	0.0-77.3	0.1-77.7	0.1-132.0	0.1-135.4	0.2-134.8	0.2-127.8	3.7-63.5	0.7-62.5	13.8-60.9	1.4-61.2	3.7-63.5	0.7-62.5
< 3 months	15 (19.7)	10 (16.4)	25 (15.4)	27 (17.0)	10 (6.4)	3 (2.4)	11 (6.4)	5 (4.8)	0	2 (11.8)	0	1 (8.3)	0	3 (10.3)
≥ 3 - < 6 months	17 (22.4)	15 (24.6)	14 (8.6)	11 (6.9)	7 (4.5)	3 (2.4)	6 (3.5)	8 (7.7)	3 (11.1)	1 (5.9)	0	1 (8.3)	3 (7.5)	2 (6.9)
≥ 6 - < 12 months	13 (17.1)	11 (18.0)	25 (15.4)	21 (13.2)	9 (5.8)	4 (3.3)	5 (2.9)	4 (3.8)	6 (22.2)	4 (23.5)	0	2 (16.7)	6 (15.0)	6 (20.7)
≥ 12 - < 18 months	10 (13.2)	7 (11.5)	19 (11.7)	18 (11.3)	8 (5.1)	8 (6.5)	8 (4.6)	1 (1.0)	2 (7.4)	1 (5.9)	2 (15.4)	1 (8.3)	4 (10.0)	2 (6.9)

Duration of exposure (months)	CAMN107A2101E1 and E2				CAMN107A2303				CAMN107A2203 and CAMN107A2120 (Pediatric population)					
	LPLV				LPLV				LPLV					
	Imatinib-resistant/intolerant				Newly diagnosed				Imatinib/ dasatinib resistant/intolerant		Newly diagnosed		All patients	
	CML-AP		CML-CP		CML-CP				Ph+ CML-CP					
	400 mg bid				300 mg bid		400 mg bid		230 mg/m^2 bid					
	Male	Female	Male	Female	Male	Female	Male	Female	Male 2 to < 12 yr	Female 12 to < 18 yr	Male 2 to < 12 yr	Female 12 to < 18 yr	Male 2 to < 12 yr	Female 12 to < 18 yr
	N=76 n (%)	N=61 n (%)	N=162 n (%)	N=159 n (%)	N=156 n (%)	N=123 n (%)	N=173 n (%)	N=104 n (%)	N=27 n (%)	N=17 n (%)	N=13 n (%)	N=12 n (%)	N=40 n (%)	N=29 n (%)
≥ 18 - < 24 months	8 (10.5)	5 (8.2)	14 (8.6)	12 (7.5)	8 (5.1)	5 (4.1)	4 (2.3)	4 (3.8)	2 (7.4)	0	0	1 (8.3)	2 (5.0)	1 (3.4)
≥ 24 - < 30 months	2 (2.6)	3 (4.9)	2 (1.2)	11 (6.9)	3 (1.9)	4 (3.3)	7 (4.0)	0	0	0	1 (7.7)	0	1 (2.5)	0
≥ 30 - < 36 months	2 (2.6)	1 (1.6)	6 (3.7)	7 (4.4)	3 (1.9)	2 (1.6)	3 (1.7)	1 (1.0)	1 (3.7)	1 (5.9)	1 (7.7)	1 (8.3)	2 (5.0)	2 (6.9)
≥ 36 - < 42 months	2 (2.6)	3 (4.9)	3 (1.9)	2 (1.3)	5 (3.2)	2 (1.6)	4 (2.3)	4 (3.8)	1 (3.7)	0	1 (7.7)	0	2 (5.0)	0
≥ 42 - < 48 months	1 (1.3)	1 (1.6)	3 (1.9)	2 (1.3)	4 (2.6)	2 (1.6)	3 (1.7)	2 (1.9)	-	-	-	-	-	-
≥ 48 - < 54 months	0	0	0	3 (1.9)	0	1 (0.8)	2 (1.2)	3 (2.9)	1 (3.7)	0	1 (7.7)	0	2 (5.0)	0
≥ 54 - < 60 months	1 (1.3)	0	8 (4.9)	3 (1.9)	7 (4.5)	10 (8.1)	6 (3.5)	4 (3.8)	0	0	2 (15.4)	0	2 (5.0)	0
≥ 60 - < 66 months	-	-	-	-	-	-	-	-	11 (40.7)	8 (47.1)	5 (38.5)	5 (41.7)	16 (40.0)	13 (44.8)
≥ 60 - < 72 months	4 (5.3)	3 (4.9)	29 (17.9)	30 (18.9)	9 (5.8)	12 (9.8)	19 (11.0)	6 (5.8)	-	-	-	-	-	-
≥ 72 - < 84 months	1 (1.3)	2 (3.3)	14 (8.6)	12 (7.5)	4 (2.6)	8 (6.5)	6 (3.5)	8 (7.7)	-	-	-	-	-	-

Duration of exposure (months)	CAMN107A2101E1 and E2				CAMN107A2303				CAMN107A2203 and CAMN107A2120 (Pediatric population)					
	LPLV				LPLV				LPLV					
	Imatinib-resistant/intolerant				Newly diagnosed				Imatinib/ dasatinib resistant/intolerant		Newly diagnosed		All patients	
	CML-AP		CML-CP		CML-CP				Ph+ CML-CP					
	400 mg bid				300 mg bid		400 mg bid		230 mg/m^2 bid					
	Male	Female	Male	Female	Male	Female	Male	Female	Male 2 to < 12 yr	Female 12 to < 18 yr	Male 2 to < 12 yr	Female 12 to < 18 yr	Male 2 to < 12 yr	Female 12 to < 18 yr
	N=76 n (%)	N=61 n (%)	N=162 n (%)	N=159 n (%)	N=156 n (%)	N=123 n (%)	N=173 n (%)	N=104 n (%)	N=27 n (%)	N=17 n (%)	N=13 n (%)	N=12 n (%)	N=40 n (%)	N=29 n (%)
≥ 84 - < 96 months	0	0	0	0	4 (2.6)	3 (2.4)	10 (5.8)	8 (7.7)	-	-	-	-	-	-
≥ 96 - < 108 months	0	0	0	0	7 (4.5)	8 (6.5)	7 (4.0)	1 (1.0)	-	-	-	-	-	-
≥ 108 - < 120 months	0	0	0	0	10 (6.4)	5 (4.1)	18 (10.4)	12 (11.5)	-	-	-	-	-	-
≥ 120 - < 132 months	0	0	0	0	58 (37.2)	42 (34.1)	52 (30.1)	33 (31.7)	-	-	-	-	-	-
≥ 132 - < 144 months	0	0	0	0	0	1 (0.8)	2 (1.2)	0	-	-	-	-	-	-
Cumulative exposure														
≥ 3 months	61 (80.3)	51 (83.6)	137 (84.6)	132 (83.0)	146 (93.6)	120 (97.6)	162 (93.6)	99 (95.2)	27 (100)	15 (88.2)	13 (100)	11 (91.7)	40 (100)	26 (89.7)
≥ 6 months	44 (57.9)	36 (59.0)	123 (75.9)	121 (76.1)	139 (89.1)	117 (95.1)	156 (90.2)	91 (87.5)	24 (88.9)	14 (82.4)	13 (100)	10 (83.3)	37 (92.5)	24 (82.8)
≥ 12 months	31 (40.8)	25 (41.0)	98 (60.5)	100 (62.9)	130 (83.3)	113 (91.9)	151 (87.3)	87 (83.7)	18 (66.7)	10 (58.8)	13 (100)	8 (66.7)	31 (77.5)	18 (62.1)

Duration of exposure (months)	CAMN107A2101E1 and E2				CAMN107A2303				CAMN107A2203 and CAMN107A2120 (Pediatric population)					
	LPLV				LPLV				LPLV					
	Imatinib-resistant/intolerant				Newly diagnosed				Imatinib/ dasatinib resistant/intolerant		Newly diagnosed		All patients	
	CML-AP		CML-CP		CML-CP				Ph+ CML-CP					
	400 mg bid				300 mg bid		400 mg bid		230 mg/m^2 bid					
	Male	Female	Male	Female	Male	Female	Male	Female	Male 2 to < 12 yr	Female 12 to < 18 yr	Male 2 to < 12 yr	Female 12 to < 18 yr	Male 2 to < 12 yr	Female 12 to < 18 yr
	N=76 n (%)	N=61 n (%)	N=162 n (%)	N=159 n (%)	N=156 n (%)	N=123 n (%)	N=173 n (%)	N=104 n (%)	N=27 n (%)	N=17 n (%)	N=13 n (%)	N=12 n (%)	N=40 n (%)	N=29 n (%)
≥ 18 months	21 (27.6)	18 (29.5)	79 (48.8)	82 (51.6)	122 (78.2)	105 (85.4)	143 (82.7)	86 (82.7)	16 (59.3)	9 (52.9)	11 (84.6)	7 (58.3)	27 (67.5)	16 (55.2)
≥ 24 months	13 (17.1)	13 (21.3)	65 (40.1)	70 (44.0)	114 (73.1)	100 (81.3)	139 (80.3)	82 (78.8)	14 (51.9)	9 (52.9)	11 (84.6)	6 (50.0)	25 (62.5)	15 (51.7)
≥ 30 months	11 (14.5)	10 (16.4)	63 (38.9)	59 (37.1)	111 (71.2)	96 (78.0)	132 (76.3)	82 (78.8)	14 (51.9)	9 (52.9)	10 (76.9)	6 (50.0)	24 (60.0)	15 (51.7)
≥ 36 months	9 (11.8)	9 (14.8)	57 (35.2)	52 (32.7)	108 (69.2)	94 (76.4)	129 (74.6)	81 (77.9)	13 (48.1)	8 (47.1)	9 (69.2)	5 (41.7)	22 (55.0)	13 (44.8)
≥ 42 months	7 (9.2)	6 (9.8)	54 (33.3)	50 (31.4)	103 (66.0)	92 (74.8)	125 (72.3)	77 (74.0)	12 (44.4)	8 (47.1)	8 (61.5)	5 (41.7)	20 (50.0)	13 (44.8)
≥ 48 months	6 (7.9)	5 (8.2)	51 (31.5)	48 (30.2)	99 (63.5)	90 (73.2)	122 (70.5)	75 (72.1)	12 (44.4)	8 (47.1)	8 (61.5)	5 (41.7)	20 (50.0)	13 (44.8)
≥ 54 months	6 (7.9)	5 (8.2)	51 (31.5)	45 (28.3)	99 (63.5)	89 (72.4)	120 (69.4)	72 (69.2)	11 (40.7)	8 (47.1)	7 (53.8)	5 (41.7)	18 (45.0)	13 (44.8)
≥ 60 months	5 (6.6)	5 (8.2)	43 (26.5)	42 (26.4)	92 (59.0)	79 (64.2)	114 (65.9)	68 (65.4)	11 (40.7)	8 (47.1)	5 (38.5)	5 (41.7)	16 (40.0)	13 (44.8)

Duration of exposure (months)	CAMN107A2101E1 and E2				CAMN107A2303				CAMN107A2203 and CAMN107A2120 (Pediatric population)					
	LPLV				LPLV				LPLV					
	Imatinib-resistant/intolerant				Newly diagnosed				Imatinib/ dasatinib resistant/intolerant		Newly diagnosed		All patients	
	CML-AP		CML-CP		CML-CP				Ph+ CML-CP					
	400 mg bid				300 mg bid		400 mg bid		230 mg/m^2 bid					
	Male	Female	Male	Female	Male	Female	Male	Female	Male 2 to < 12 yr	Female 12 to < 18 yr	Male 2 to < 12 yr	Female 12 to < 18 yr	Male 2 to < 12 yr	Female 12 to < 18 yr
	N=76 n (%)	N=61 n (%)	N=162 n (%)	N=159 n (%)	N=156 n (%)	N=123 n (%)	N=173 n (%)	N=104 n (%)	N=27 n (%)	N=17 n (%)	N=13 n (%)	N=12 n (%)	N=40 n (%)	N=29 n (%)
≥ 72 months	1 (1.3)	2 (3.3)	14 (8.6)	12 (7.5)	83 (53.2)	67 (54.5)	95 (54.9)	62 (59.6)	-	-	-	-	-	-
≥ 84 months	0	0	0	0	79 (50.6)	59 (48.0)	89 (51.4)	54 (51.9)	-	-	-	-	-	-
≥ 96 months	0	0	0	0	75 (48.1)	56 (45.5)	79 (45.7)	46 (44.2)	-	-	-	-	-	-
≥ 108 months	0	0	0	0	68 (43.6)	48 (39.0)	72 (41.6)	45 (43.3)	-	-	-	-	-	-
≥ 120 months	0	0	0	0	58 (37.2)	43 (35.0)	54 (31.2)	33 (31.7)	-	-	-	-	-	-
≥ 132 months	0	0	0	0	0	1 (0.8)	2 (1.2)	0	-	-	-	-	-	-
Total patient-months	1157.48	988.81	4871.34	4777.95	11696.88	9682.56	13509.57	8133.84	939.40	585.60	594.50	398.00	1533.90	983.60

- Exposure (months) = (last date of study drug - start date of study drug +1)/30.4375 (i.e., interruption periods are also included in the calculation of exposure).
- Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (months).
- One patient in the CML-AP group with missing imatinib-resistance/intolerance criteria at baseline was included in the analysis.

Source: [Annex 7–Table 12-3] and [Annex 7-Table 1.2-3p].

Table 4-4 Exposure by gender (Study CAMN107A2109 (ENACT Study))

Duration of exposure (months)	CAMN107A2109 (ENACT Study)			
	Imatinib-resistant/ intolerant			
	LPLV			
	CML-AP (400 mg bid)		CML-CP (400 mg bid)	
	Male	Female	Male	Female
	N=104 n (%)	N=77 n (%)	N=696 n (%)	N=726 n (%)
Mean (SD)	7.59 (6.23)	7.16 (6.61)	9.67 (6.38)	9.42 (6.51)
Median	5.67	4.37	8.92	8.53
Range	0.2-24.2	0.3-22.3	0.0-26.2	0.0-26.5
< 3 months	27 (26.0)	30 (39.0)	125 (18.0)	141 (19.4)
≥ 3 - < 6 months	28 (26.9)	14 (18.2)	128 (18.4)	134 (18.5)
≥ 6 - < 12 months	24 (23.1)	13 (16.9)	190 (27.3)	200 (27.5)
≥ 12 - < 18 months	17 (16.3)	13 (16.9)	165 (23.7)	152 (20.9)
≥ 18 - < 24 months	7 (6.7)	7 (9.1)	80 (11.5)	92 (12.7)
≥ 24 - < 30 months	1 (1.0)	0	8 (1.1)	7 (1.0)
Cumulative exposure				
≥ 3 months	77 (74.0)	47 (61.0)	571 (82.0)	585 (80.6)
≥ 6 months	49 (47.1)	33 (42.9)	443 (63.6)	451 (62.1)
≥ 12 months	25 (24.0)	20 (26.0)	253 (36.4)	251 (34.6)
≥ 18 months	8 (7.7)	7 (9.1)	88 (12.6)	99 (13.6)
≥ 24 months	1 (1.0)	0	8 (1.1)	7 (1.0)
Total patient-months	788.96	551.59	6731.40	6835.55

- Exposure (months) = (last date of study drug - start date of study drug +1)/30.4375 (i.e., interruption periods are also included in the calculation of exposure).
- Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (months).
- One patient in the CML-AP group with missing imatinib-resistance/intolerance criteria at baseline was included in the analysis.

Source: [Annex 7–Table 12-7]

Table 4-5 Exposure by race (Studies CAMN107A2101E1 and E2, CAMN107A2303 and CAMN107A2109 (ENACT study))

	CAMN107A2101E1 and E2		CAMN107A2303		CAMN107A2109 (ENACT Study)	
	Imatinib-resistant/intolerant		Newly diagnosed		Imatinib-resistant/intolerant	
	LPLV		LPLV		LPLV	
	CML-AP	CML-CP	CML-CP		CML-AP	CML-CP*
	400 mg bid.		300 mg bid.	400 mg bid.	400 mg bid.	
Duration of exposure (months)	**N=137 n (%)**	**N=321 n (%)**	**N=279 n (%)**	**N=277 n (%)**	**N=181 n (%)**	**N=1422 n (%)**
Caucasian	**n=109**	**n=297**	**n=169**	**n=183**	**n=113**	**n=1029**
Mean (SD)	16.96 (20.00)	29.73 (27.33)	73.16 (44.32)	75.35 (43.01)	7.18 (6.36)	9.53 (6.53)
Median	8.94	17.97	76.16	81.48	4.99	8.34
Range	0.1-75.7	0.0-77.7	0.1-132.0	0.2-134.8	0.2-24.2	0.0-26.5
< 3 months	21 (19.3)	49 (16.5)	8 (4.7)	12 (6.6)	36 (31.9)	200 (19.4)
≥ 3 - < 6 months	23 (21.1)	21 (7.1)	5 (3.0)	9 (4.9)	27 (23.9)	199 (19.3)
≥ 6 - < 12 months	19 (17.4)	44 (14.8)	8 (4.7)	2 (1.1)	25 (22.1)	252 (24.5)
≥ 12 - < 18 months	12 (11.0)	35 (11.8)	7 (4.1)	8 (4.4)	16 (14.2)	234 (22.7)
≥ 18 - < 24 months	11 (10.1)	24 (8.1)	10 (5.9)	4 (2.2)	8 (7.1)	135 (13.1)
≥ 24 - < 30 months	4 (3.7)	13 (4.4)	7 (4.1)	3 (1.6)	1 (0.9)	9 (0.9)
≥ 30 - < 36 months	2 (1.8)	13 (4.4)	2 (1.2)	3 (1.6)	0	0
≥ 36 - < 42 months	4 (3.7)	5 (1.7)	5 (3.0)	6 (3.3)	0	0
≥ 42 - < 48 months	2 (1.8)	5 (1.7)	5 (3.0)	5 (2.7)	0	0
≥ 48 - < 54 months	0	2 (0.7)	0	3 (1.6)	0	0
≥ 54 - < 60 months	1 (0.9)	9 (3.0)	11 (6.5)	9 (4.9)	0	0
≥ 60 - < 72 months	7 (6.4)	52 (17.5)	15 (8.9)	19 (10.4)	0	0
≥ 72 - < 84 months	3 (2.8)	25 (8.4)	12 (7.1)	13 (7.1)	0	0
≥ 84 - < 96 months	0	0	6 (3.6)	15 (8.2)	0	0
≥ 96 - < 108 months	0	0	10 (5.9)	7 (3.8)	0	0
≥ 108 - <120 months	0	0	12 (7.1)	27 (14.8)	0	0
≥ 120 - <132 months	0	0	46 (27.2%)	37 (20.2)	0	0
≥ 132 - <144 months	0	0	0	1 (0.5)	0	0

	CAMN107A2101E1 and E2		CAMN107A2303		CAMN107A2109 (ENACT Study)	
	Imatinib-resistant/intolerant		Newly diagnosed		Imatinib-resistant/intolerant	
	LPLV		LPLV		LPLV	
	CML-AP	CML-CP	CML-CP		CML-AP	CML-CP*
	400 mg bid.		300 mg bid.	400 mg bid.	400 mg bid.	
Duration of exposure (months)	**N=137 n (%)**	**N=321 n (%)**	**N=279 n (%)**	**N=277 n (%)**	**N=181 n (%)**	**N=1422 n (%)**
Cumulative exposure						
≥ 3 months	88 (80.7)	248 (83.5)	161 (95.3)	171 (93.4)	77 (68.1)	829 (80.6)
≥ 6 months	65 (59.6)	227 (76.4)	156 (92.3)	162 (88.5)	50 (44.2)	630 (61.2)
≥ 12 months	46 (42.2)	183 (61.6)	148 (87.6)	160 (87.4)	25 (22.1)	378 (36.7)
≥ 18 months	34 (31.2)	148 (49.8)	141 (83.4)	152 (83.1)	9 (8.0)	144 (14.0)
≥ 24 months	23 (21.1)	124 (41.8)	131 (77.5)	148 (80.9)	1 (0.9)	9 (0.9)
≥ 30 months	19 (17.4)	111 (37.4)	124 (73.4)	145 (79.2)	0	0
≥ 36 months	17 (15.6)	98 (33.0)	122 (72.2)	142 (77.6)	0	0
≥ 42 months	13 (11.9)	93 (31.3)	117 (69.2)	136 (74.3)	0	0
≥ 48 months	11 (10.1)	88 (29.6)	112 (66.3)	131 (71.6)	0	0
≥ 54 months	11 (10.1)	86 (29.0)	112 (66.3)	128 (69.9)	0	0
≥ 60 months	10 (9.2)	77 (25.9)	101 (59.8)	119 (65.0)	0	0
≥ 72 months	3 (2.8)	25 (8.4)	86 (50.9)	100 (54.6)	0	0
≥ 84 months	0	0	74 (43.8)	87 (47.5)	0	0
≥ 96 months	0	0	68 (40.2)	72 (39.3)	0	0
≥ 108 months	0	0	58 (34.3)	65 (35.5)	0	0
≥ 120 months	0	0	46 (27.2)	38 (20.8)	0	0
≥ 132 months	0	0	0	1 (0.5)	0	0
Total patient-months	1848.64	8829.81	12364.04	13789.05	811.86	9806.62
Black	**n=9**	**n=15**	**n=12**	**n=11**	**n=9**	**n=47**
Mean (SD)	12.98 (13.97)	33.46 (30.81)	80.98 (51.45)	64.16 (56.67)	7.43 (6.25)	8.90 (5.93)
Median	5.75	20.50	120.36	36.27	6.28	8.61
Range	1.0-40.0	0.5-72.9	14.3-125.6	3.7-124.6	0.5-18.5	0.7-20.6

	CAMN107A2101E1 and E2		CAMN107A2303		CAMN107A2109 (ENACT Study)	
	Imatinib-resistant/intolerant		Newly diagnosed		Imatinib-resistant/intolerant	
	LPLV		LPLV		LPLV	
	CML-AP	CML-CP	CML-CP		CML-AP	CML-CP*
	400 mg bid.		300 mg bid.	400 mg bid.	400 mg bid.	
Duration of exposure (months)	**N=137 n (%)**	**N=321 n (%)**	**N=279 n (%)**	**N=277 n (%)**	**N=181 n (%)**	**N=1422 n (%)**
< 3 months	1 (11.1)	3 (20.0)	0	0	3 (33.3)	11 (23.4)
≥ 3 - < 6 months	4 (44.4)	0	0	2 (18.2)	1 (11.1)	6 (12.8)
≥ 6 - < 12 months	1 (11.1)	2 (13.3)	0	2 (18.2)	2 (22.2)	13 (27.7)
≥ 12 - < 18 months	1 (11.1)	2 (13.3)	4 (33.3)	0	2 (22.2)	14 (29.8)
≥ 18 - < 24 months	0	2 (13.3)	0	0	1 (11.1)	3 (6.4)
≥ 24 - < 30 months	0	0	0	1 (9.1)	0	0
≥ 30 - < 36 months	1 (11.1)	0	0	0	0	0
≥ 36 - < 42 months	1 (11.1)	0	0	1 (9.1)	0	0
≥ 54 - < 60 months	0	0	1 (8.3)	0	0	0
≥ 60 - < 72 months	0	5 (33.3)	0	0	0	0
≥ 72 - < 84 months	0	1 (6.7)	0	0	0	0
≥ 120 - < 132 months	0	0	7 (58.3)	5 (45.5)	0	0
Cumulative exposure						
≥ 3 months	8 (88.9)	12 (80.0)	12 (100)	11 (100)	6 (66.7)	36 (76.6)
≥ 6 months	4 (44.4)	12 (80.0)	12 (100)	9 (81.8)	5 (55.6)	30 (63.8)
≥ 12 months	3 (33.3)	10 (66.7)	12 (100)	7 (63.6)	3 (33.3)	17 (36.2)
≥ 18 months	2 (22.2)	8 (53.3)	8 (66.7)	7 (63.6)	1 (11.1)	3 (6.4)
≥ 24 months	2 (22.2)	6 (40.0)	8 (66.7)	7 (63.6)	0	0
≥ 30 months	2 (22.2)	6 (40.0)	8 (66.7)	6 (54.5)	0	0
≥ 36 months	1 (11.1)	6 (40.0)	8 (66.7)	6 (54.5)	0	0
≥ 42 months	0	6 (40.0)	8 (66.7)	5 (45.5)	0	0
≥ 48 months	0	6 (40.0)	8 (66.7)	5 (45.5)	0	0
≥ 54 months	0	6 (40.0)	8 (66.7)	5 (45.5)	0	0

	CAMN107A2101E1 and E2		CAMN107A2303		CAMN107A2109 (ENACT Study)	
	Imatinib-resistant/intolerant		Newly diagnosed		Imatinib-resistant/intolerant	
	LPLV		LPLV		LPLV	
	CML-AP	CML-CP	CML-CP		CML-AP	CML-CP*
	400 mg bid.		300 mg bid.	400 mg bid.	400 mg bid.	
Duration of exposure (months)	**N=137 n (%)**	**N=321 n (%)**	**N=279 n (%)**	**N=277 n (%)**	**N=181 n (%)**	**N=1422 n (%)**
≥ 60 months	0	6 (40.0)	7 (58.3)	5 (45.5)	0	0
≥ 72 months	0	1 (6.7)	7 (58.3)	5 (45.5)	0	0
≥ 84 months	0	0	7 (58.3)	5 (45.5)	0	0
≥ 96 months	0	0	7 (58.3)	5 (45.5)	0	0
≥ 108 months	0	0	7 (58.3)	5 (45.5)	0	0
≥ 120 months	0	0	7 (58.3)	5 (45.5)	0	0
Total patient-months	116.82	501.90	971.76	705.76	66.89	418.46
Asian	**n=15**	**n=5**	**n=74**	**n=64**	**n=46**	**n=277**
Mean (SD)	9.48 (6.79)	36.48 (29.76)	89.37 (47.71)	91.09 (46.40)	7.67 (6.37)	10.11 (6.48)
Median	9.99	48.33	121.02	121.25	5.42	9.63
Range	0.4-21.5	4.5-67.1	1.2-127.6	0.3-130.9	0.5-21.9	0.0-26.2
< 3 months	3 (20.0)	0	4 (5.4)	3 (4.7)	13 (28.3)	41 (14.8)
≥ 3 - < 6 months	3 (20.0)	2 (40.0)	3 (4.1)	1 (1.6)	11 (23.9)	47 (17.0)
≥ 6 - < 12 months	3 (20.0)	0	3 (4.1)	4 (6.3)	9 (19.6)	91 (32.9)
≥ 12 - < 18months	4 (26.7)	0	4 (5.4)	0	10 (21.7)	59 (21.3)
≥ 18 - < 24 months	2 (13.3)	0	1 (1.4)	4 (6.3)	3 (6.5)	34 (12.3)
≥ 24 - < 30 months	0	0	0	1 (1.6)	0	5 (1.8)
≥ 30 - < 36 months	0	0	1 (1.4)	1 (1.6)	0	0
≥ 36 - < 42 months	0	0	2 (2.7)	1 (1.6)	0	0
≥ 42 - < 48 months	0	0	1 (1.4)	0	0	0
≥ 48 - < 54 months	0	1 (20.0)	0	2 (3.1)	0	0
≥ 54 - < 60 months	0	1 (20.0)	2 (2.7)	0	0	0
≥ 60 - < 72 months	0	1 (20.0)	3 (4.1)	4 (6.3)	0	0

	CAMN107A2101E1 and E2		CAMN107A2303		CAMN107A2109 (ENACT Study)	
	Imatinib-resistant/intolerant		Newly diagnosed		Imatinib-resistant/intolerant	
	LPLV		LPLV		LPLV	
	CML-AP	CML-CP	CML-CP		CML-AP	CML-CP*
	400 mg bid.		300 mg bid.	400 mg bid.	400 mg bid.	
Duration of exposure (months)	**N=137 n (%)**	**N=321 n (%)**	**N=279 n (%)**	**N=277 n (%)**	**N=181 n (%)**	**N=1422 n (%)**
≥ 84 - < 96 months	0	0	1 (1.4)	2 (3.1)	0	0
≥ 96 - < 108 months	0	0	5 (6.8)	1 (1.6)	0	0
≥ 108 - < 120 months	0	0	2 (2.7)	3 (4.7)	0	0
≥ 120 - < 132 months	0	0	42 (56.8)	37 (57.8)	0	0
Cumulative exposure						
≥ 3 months	12 (80.0)	5 (100)	70 (94.6)	61 (95.3)	33 (71.7)	236 (85.2)
≥ 6 months	9 (60.0)	3 (60.0)	67 (90.5)	60 (93.8)	22 (47.8)	189 (68.2)
≥ 12 months	6 (40.0)	3 (60.0)	64 (86.5)	56 (87.5)	13 (28.3)	98 (35.4)
≥ 18 months	2 (13.3)	3 (60.0)	60 (81.1)	56 (87.5)	3 (6.5)	39 (14.1)
≥ 24 months	0	3 (60.0)	59 (79.7)	52 (81.3)	0	5 (1.8)
≥ 30 months	0	3 (60.0)	59 (79.7)	51 (79.7)	0	0
≥ 36 months	0	3 (60.0)	58 (78.4)	50 (78.1)	0	0
≥ 42 months	0	3 (60.0)	56 (75.7)	49 (76.6)	0	0
≥ 48 months	0	3 (60.0)	55 (74.3)	49 (76.6)	0	0
≥ 54 months	0	2 (40.0)	55 (74.3)	47 (73.4)	0	0
≥ 60 months	0	1 (20.0)	53 (71.6)	47 (73.4)	0	0
≥ 72 months	0	0	50 (67.6)	43 (67.2)	0	0
≥ 84 months	0	0	50 (67.6)	43 (67.2)	0	0
≥ 96 months	0	0	49 (66.2)	41 (64.1)	0	0
≥ 108 months	0	0	44 (59.5)	40 (62.5)	0	0
≥ 120 months	0	0	42 (56.8)	37 (57.8)	0	0
Total patient-months	142.20	182.40	6613.38	5829.76	352.95	2799.24

	CAMN107A2101E1 and E2		CAMN107A2303		CAMN107A2109 (ENACT Study)	
	Imatinib-resistant/intolerant		Newly diagnosed		Imatinib-resistant/intolerant	
	LPLV		LPLV		LPLV	
	CML-AP	CML-CP	CML-CP		CML-AP	CML-CP*
	400 mg bid.		300 mg bid.	400 mg bid.	400 mg bid.	
Duration of exposure (months)	**N=137 n (%)**	**N=321 n (%)**	**N=279 n (%)**	**N=277 n (%)**	**N=181 n (%)**	**N=1422 n (%)**
Other	**n=4**	**n=4**	**n=24**	**n=19**	**n=13**	**n=68**
Mean (SD)	9.57 (10.50)	33.83 (35.18)	59.62 (47.03)	69.44 (50.81)	8.37 (7.31)	7.76 (4.95)
Median	4.99	30.19	56.48	68.67	4.44	7.56
Range	3.2-25.1	3.0-71.9	0.1-135.4	0.3-133.4	0.9-22.3	0.1-24.6
< 3 months	0	0	1 (4.2)	1 (5.3)	5 (38.5)	14 (20.6)
≥ 3 - < 6 months	2 (50.0)	2 (50.0)	2 (8.3)	2 (10.5)	3 (23.1)	10 (14.7)
≥ 6 - < 12 months	1 (25.0)	0	2 (8.3)	1 (5.3)	1 (7.7)	34 (50.0)
≥ 12 - < 18 months	0	0	1 (4.2)	1 (5.3)	2 (15.4)	9 (13.2)
≥ 18 - < 24 months	0	0	2 (8.3)	0	2 (15.4)	0
≥ 24 - < 30 months	1 (25.0)	0	0	2 (10.5)	0	1 (1.5)
≥ 30 - < 36 months	0	0	2 (8.3)	0	0	0
≥ 48 - < 54 months	0	0	1 (4.2)	0	0	0
≥ 54 - < 60 months	0	1 (25.0)	3 (12.5)	1 (5.3)	0	0
≥ 60 - < 72 months	0	1 (25.0)	3 (12.5)	2 (10.5)	0	0
≥ 72 - < 84 months	0	0	0	1 (5.3)	0	0
≥ 84 - < 96 months	0	0	0	1 (5.3)	0	0
≥ 108 - < 120 months	0	0	1 (4.2)	0	0	0
≥ 120 - < 132 months	0	0	5 (20.8)	6 (31.6)	0	0
≥ 132 - < 144 months	0	0	1 (4.2)	1 (5.3)	0	0
Cumulative exposure						
≥ 3 months	4 (100)	4 (100)	23 (95.8)	18 (94.7)	8 (61.5)	54 (79.4)
≥ 6 months	2 (50.0)	2 (50.0)	21 (87.5)	16 (84.2)	5 (38.5)	44 (64.7)
≥ 12 months	1 (25.0)	2 (50.0)	19 (79.2)	15 (78.9)	4 (30.8)	10 (14.7)

	CAMN107A2101E1 and E2		CAMN107A2303		CAMN107A2109 (ENACT Study)	
	Imatinib-resistant/intolerant		Newly diagnosed		Imatinib-resistant/intolerant	
	LPLV		LPLV		LPLV	
	CML-AP	CML-CP	CML-CP		CML-AP	CML-CP*
	400 mg bid.		300 mg bid.	400 mg bid.	400 mg bid.	
Duration of exposure (months)	**N=137 n (%)**	**N=321 n (%)**	**N=279 n (%)**	**N=277 n (%)**	**N=181 n (%)**	**N=1422 n (%)**
≥ 18 months	1 (25.0)	2 (50.0)	18 (75.0)	14 (73.7)	2 (15.4)	1 (1.5)
≥ 24 months	1 (25.0)	2 (50.0)	16 (66.7)	14 (73.7)	0	1 (1.5)
≥ 30 months	0	2 (50.0)	16 (66.7)	12 (63.2)	0	0
≥ 36 months	0	2 (50.0)	14 (58.3)	12 (63.2)	0	0
≥ 42 months	0	2 (50.0)	14 (58.3)	12 (63.2)	0	0
≥ 48 months	0	2 (50.0)	14 (58.3)	12 (63.2)	0	0
≥ 54 months	0	2 (50.0)	13 (54.2)	12 (63.2)	0	0
≥ 60 months	0	1 (25.0)	10 (41.7)	11 (57.9)	0	0
≥ 72 months	0	0	7 (29.2)	9 (47.4)	0	0
≥ 84 months	0	0	7 (29.2)	8 (42.1)	0	0
≥ 96 months	0	0	7 (29.2)	8 (42.1)	0	0
≥ 108 months	0	0	7 (29.2)	7 (36.8)	0	0
≥ 120 months	0	0	6 (25.0)	7 (36.8)	0	0
≥ 132 months	0	0	1 (4.2)	1 (5.3)	0	0
Total patient-months	38.28	135.32	1430.88	1319.36	108.85	527.74
Unknown					**n=0**	**n=1**
Mean (SD)	-	-	-	-	-	14.88
Median	-	-	-	-	-	14.88
Range	-	-	-	-	-	14.9-14.9
≥ 12 - < 18 months	-	-	-	-	-	1 (100)
Cumulative exposure						
≥ 3 months	-	-	-	-	0	1 (100)
≥ 6 months	-	-	-	-	0	1 (100)

	CAMN107A2101E1 and E2		CAMN107A2303		CAMN107A2109 (ENACT Study)	
	Imatinib-resistant/intolerant		Newly diagnosed		Imatinib-resistant/intolerant	
	LPLV		LPLV		LPLV	
	CML-AP	CML-CP	CML-CP		CML-AP	CML-CP*
	400 mg bid.		300 mg bid.	400 mg bid.	400 mg bid.	
Duration of exposure (months)	**N=137 n (%)**	**N=321 n (%)**	**N=279 n (%)**	**N=277 n (%)**	**N=181 n (%)**	**N=1422 n (%)**
≥ 12 months	-	-	-	-	0	1 (100)
Total patient-months	-	-	-	-	0	14.88

- Exposure (months) = (last date of study drug - start date of study drug +1)/30.4375 (i.e., interruption periods are also included in the calculation of exposure).
- Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (months).
- One patient in the CML-AP group with missing imatinib-resistance/intolerance criteria at baseline was included in the analysis.

Source: [Annex 7-Table 12-4] and [Annex 7-Table 12-8]

Table 4-6 Exposure by race (Study CAMN107A2203 and CAMN107A2120)

	CAMN107A2203 and CAMN107A2120 (Pediatric population)					
	LPLV					
	Imatinib/dasatinib resistant/intolerant		Newly diagnosed		All patients	
	Ph+ CML-CP (230 mg/m^2 bid)					
Duration of exposure (months)	**Caucasian (N=21) n (%)**	**Asian (N=17) n (%)**	**Caucasian (N=18) n (%)**	**Asian (N=7) n (%)**	**Caucasian (N=39) n (%)**	**Asian (N=24) n (%)**
Mean (SD)	31.49 (24.87)	40.52 (25.63)	34.89 (24.48)	52.07 (10.38)	33.06 (24.42)	43.89 (22.67)
Median	22.08	60.48	29.80	55.39	27.60	60.48
Range	2.4-63.5	0.7-61.0	1.4-61.2	35.8-60.6	1.4-63.5	0.7-61.0
<3 months	1 (4.8)	1 (5.9)	1 (5.6)	0	2 (5.1)	1 (4.2)
3 - < 6 months	3 (14.3)	0	1 (5.6)	0	4 (10.3)	0
6 - < 12 months	5 (23.8)	4 (23.5)	2 (11.1)	0	7 (17.9)	4 (16.7)
12 - < 18 months	1 (4.8)	1 (5.9)	3 (16.7)	0	4 (10.3)	1 (4.2)
18 - < 24 months	1 (4.8)	0	1 (5.6)	0	2 (5.1)	0
24 - < 30 months	0	0	1 (5.6)	0	1 (2.6)	0

	CAMN107A2203 and CAMN107A2120 (Pediatric population)					
	LPLV					
	Imatinib/dasatinib resistant/intolerant		Newly diagnosed		All patients	
	Ph+ CML-CP (230 mg/m^2 bid)					
Duration of exposure (months)	**Caucasian (N=21) n (%)**	**Asian (N=17) n (%)**	**Caucasian (N=18) n (%)**	**Asian (N=7) n (%)**	**Caucasian (N=39) n (%)**	**Asian (N=24) n (%)**
30 - < 36 months	1 (4.8)	1 (5.9)	1 (5.6)	1 (14.3)	2 (5.1)	2 (8.3)
36 - < 42 months	1 (4.8)	0	0	1 (14.3)	1 (2.6)	1 (4.2)
42 - < 48 months	-	-	-	-	-	-
48 - < 54 months	1 (4.8)	0	0	1 (14.3)	1 (2.6)	1 (4.2)
54 - < 60 months	0	0	1 (5.6)	1 (14.3)	1 (2.6)	1 (4.2)
60 - < 66 months	7 (33.3)	10 (58.8)	7 (38.9)	3 (42.9)	14 (35.9)	13 (54.2)
Cumulative exposure						
≥ 3 months	20 (95.2)	16 (94.1)	17 (94.4)	7 (100)	37 (94.9)	23 (95.8)
≥ 6 months	17 (81.0)	16 (94.1)	16 (88.9)	7 (100)	33 (84.6)	23 (95.8)
≥ 12 months	12 (57.1)	12 (70.6)	14 (77.8)	7 (100)	26 (66.7)	19 (79.2)
≥ 18 months	11 (52.4)	11 (64.7)	11 (61.1)	7 (100)	22 (56.4)	18 (75.0)
≥ 24 months	10 (47.6)	11 (64.7)	10 (55.6)	7 (100)	20 (51.3)	18 (75.0)
≥ 30 months	10 (47.6)	11 (64.7)	9 (50.0)	7 (100)	19 (48.7)	18 (75.0)
≥ 36 months	9 (42.9)	10 (58.8)	8 (44.4)	6 (85.7)	17 (43.6)	16 (66.7)
≥ 42 months	8 (38.1)	10 (58.8)	8 (44.4)	5 (71.4)	16 (41.0)	15 (62.5)
≥ 48 months	8 (38.1)	10 (58.8)	8 (44.4)	5 (71.4)	16 (41.0)	15 (62.5)
≥ 54 months	7 (33.3)	10 (58.8)	8 (44.4)	4 (57.1)	15 (38.5)	14 (58.3)
≥ 60 months	7 (33.3)	10 (58.8)	7 (38.9)	3 (42.9)	14 (35.9)	13 (54.2)
Total patient-months	661.4	688.9	628.0	364.5	1289.4	1053.4

- Exposure (months) = (last date of study drug - start date of study drug +1)/30.4375 (i.e., interruption periods are also included in the calculation of exposure)
- Patient-months are derived by taking the number of patients multiplied by the mean duration of exposure (months).
Source: [Annex 7-Table 1.2-4p].

5 Part II Safety specification Module SIV: Populations not studied in clinical trials

5.1 Part II Module SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Table 5-1 Important exclusion criteria in pivotal studies in the development program

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
-- Inability to determine the QT interval on Electrocardiogram (ECG) -- Complete left bundle branch block -- Right bundle branch block plus left anterior or posterior hemiblock -- Use of a ventricular-paced pacemaker -- Congenital long QT syndrome or a known family history of long QT syndrome -- History of or presence of clinically significant ventricular or atrial tachyarrhythmias -- Clinically significant resting bradycardia -- QTc > 450 msec on the average of three serial baseline ECG using the QT interval corrected by Fridericia's formulae (QTcF). If QTcF > 450 msec and electrolytes are not within normal ranges, electrolytes should be corrected and then the patient re-tested for QTc. -- History or clinical signs of myocardial infarction within 1 year of study entry. -- History of unstable angina within 1 year of study entry -- Other clinically significant heart disease (e.g., congestive heart failure, cardiomyopathy, or uncontrolled hypertension).	These are precautionary measures to preclude enrolling patients in clinical studies who might be placed at risk after nilotinib exposure permitting interpretation and identification of the occurrence of QT prolongation.	No	Section 4.4 of the SmPC cautions use of nilotinib in patients who are at a significant risk of developing QTc prolongation. Close ECG monitoring is recommended. Drugs which are potent inducers of CYP3A4 should be used with caution. Section 4.5 of the SmPC recommends caution during the usage of anti-arrhythmic medicinal products and other substances that may prolong the QT interval.
History of acute pancreatitis within one year of study entry or past medical history of chronic pancreatitis.	Nilotinib may induce pancreatitis and also induce elevations in lipase.	No	Statements in the SmPC section 4.4 (Special warnings and precautions for use) describe elevation in serum

Criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale for not including as missing information
			lipase as an observation with nilotinib treatment. Further, caution is recommended in patients with previous history of pancreatitis. In case lipase elevations are accompanied by abdominal symptoms, nilotinib should be interrupted and appropriate diagnostic measures considered to exclude pancreatitis.
Patients actively receiving therapy with herbal medicines that are strong CYP3A4 inhibitors and/or inducers, and the treatment cannot be either discontinued or switched to a different medication prior to starting study drug. These herbal medicines may include Echinacea, (including *E. purpurea, E. angustifolia* and *E. pallida*), Piperine, Artemisinin, St. John's wort, and Ginkgo.	Concomitant medications that are strong CYP3A4 inhibitors may increase the serum levels of nilotinib and increase the risk of QT prolongation, or inducers that may conversely lower the serum levels of nilotinib and reduce clinical effectiveness.	No	Statements in the SmPC Section 4.4 (Special warnings and precautions for use) and Section 4.5 (Interaction with other medicinal products and other forms of interaction) cover in detail the effects of substances that may either increase or decrease the serum concentrations of nilotinib.
Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection, or gastric bypass surgery).	Clinical trials require appropriate precaution in order to ensure study subjects are receiving and absorbing study drug in order to render an accurate benefit-risk profile.	No	Statements in the SmPC Section 4.4 (Special warnings and precautions for use "Total gastrectomy") and Section 5.2 (Pharmacokinetic properties) explain that the bioavailability of nilotinib might be reduced in patients with total gastrectomy and that nilotinib absorption might be reduced by approximately 48% and 22% in patients with total gastrectomy and partial gastrectomy, respectively.

5.2 Part II Module SIV.2. Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

5.3 Part II Module SIV.3. Limitations in respect to populations typically underrepresented in clinical trial development programs

Table 5-2 Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Pregnant and breast feeding women	Not included in the clinical development program
Pediatric patients	Refer to Section 4.1 for exposure in pediatric patients
Patients with relevant comorbidities: • Patients with hepatic impairment	Not included in the clinical development program. However, a study (Study CAMN107A2116) in subjects with hepatic impairment (but no underlying malignancy) was performed to assess the pharmacokinetics (PK) of nilotinib in these subjects.
• Patients with renal impairment	Not clinically relevant since nilotinib and its metabolites are not excreted by the kidney.
• Patients with cardiovascular impairment	Not included in the clinical development program
Population with relevant different ethnic origin	Refer to Table 4-5 for exposure in different ethnicities.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program

6 Part II Safety specification Module SV: Post-authorization experience

6.1 Part II Module SV.1. Post-authorization exposure

Post-marketing (non-study) exposure for Tasigna is provided in the below sections through 31-Jan-2020.

6.1.1 Part II Module SV.1.1 Method used to calculate exposure

An estimate of patient exposure is calculated based on worldwide sales volume in milligrams (mg) of active substance sold and the maximum recommended daily dose of 800 mg. The cumulative patient exposure since the IBD of the product is estimated to be approximately 266,768 patient years (PTY).

6.1.2 Part II Module SV.1.2. Exposure

Table 6-1 Cumulative exposure from marketing experience

	EEA	USA and Canada	Japan	ROW
Overall	79,164 PTY	46,466 PTY	24,138 PTY	117,000 PTY

ROW: Rest of the World; USA: United States of America.
This table includes cumulative data obtained from IBD (24-Jul-2007) to this PSUR DLP (31-Jan-2020).
Source of data: PSUR (reporting period: 01-Feb-2019 to 31-Jan-2020).

Table 6-2 Estimated post-marketing (non-clinical trial) exposure, per formulation

Capsule strength	Cumulative Until 31-Jan-2020	
	Amount sold (mg)	**Estimated exposure**
50 mg	5,793,200	20 PTY
150 mg	30,246,838,615	103,585 PTY
200 mg	47,643,504,762	163,163 PTY
Total	**77,896,136,577**	**266,768 PTY**

This table includes cumulative data obtained from IBD (24-Jul-2007) through (31-Jan-2020).
Source of data: PSUR (reporting period: 01-Feb-2019 to 31-Jan-2020)

7 Part II Safety specification Module SVI: Additional EU requirements for the safety specification

7.1 Potential for misuse for illegal purposes

Based on the mechanism of action of nilotinib, a potential for abuse and dependence is not anticipated.

8 Part II Safety specification Module SVII: Identified and potential risks

8.1 Part II Module SVII.1. Identification of safety concerns in the initial RMP submission

This section is not applicable as this is not the initial RMP.

8.1.1 Part II Module SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

8.1.2 Part II Module SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

8.2 Part II Module SVII.2: New safety concerns and reclassification with a submission of an updated RMP

Table 8-1 Description of the changes done in the list of the safety concerns since the previous RMP version

Safety concerns	Previous Classification	Reclassification or Removed	Rationale
Long-term follow-up in pediatric patients	Missing information	Removed	Results from Study CAMN107A2203 (final 66-cycle analysis) showed sustained long-term efficacy and consistent long-term safety profile of nilotinib in pediatric patients with both, newly diagnosed Ph+ CML in CP and with Ph+ CML in CP resistant or intolerant to either imatinib or dasatinib that can be reliably managed by routine monitoring of clinical and laboratory examination, and appropriate dose modification according to the approved product information, as is the case for adult patients and as reported previously. Based on sustained efficacy and long-term safety data, Novartis proposes to retire 'long term follow-up in pediatric patients' from the list of missing information in the EU-RMP. However, this topic will continue to be reviewed in the Tasigna PSURs.

8.3 Part II Module SVII.3: Details of important identified risks, important potential risks, and missing information

8.3.1 Part II Module SVII.3.1. Presentation of important identified risks and important potential risks

8.3.1.1 Important identified risk: Significant bleeding

Table 8-2 Clinical trial data of significant bleeding

Risk	**Significant bleeding**							
Frequency with 95% CI and Severity and nature of risk Seriousness/outcomes		**CAMN107A2101**		**CAMN107A2303**		**CAMN107A2203 and CAMN107A2120* (Pediatric population)**		
		LPLV**		**LPLV**		**LPLV**		
		Imatinib resistant/intolerant		**Newly diagnosed**		**Imatinib/ dasatinib/ resistant/intolerant**	**Newly diagnosed**	**All patients**
		CML-AP	**CML-CP**	**CML-CP**		**CML-CP**		
		400 mg bid		**300 mg bid**	**400 mg bid**	**230 mg/m² bid**		
		N=137	**N=321**	**N=279**	**N=277**	**N=44**	**N=25**	**N=69**
	Significant Bleeding	**n (%) (95% CI)**	**n (%) (95% CI)**	**n (%) (95% CI)**	**n (%) (95% CI)**	**n (%) (95% CI)**	**n (%) (95% CI)**	**n (%) (95% CI)**
	All Adverse events (AEs)	9 (6.6) (3.0; 12.1)	11 (3.4) (1.7; 6.0)	11 (3.9) (2.0; 6.9)	20 (7.2) (4.5; 10.9)	-	-	-
	Grade 3/4 AEs	4 (2.9) (0.8; 7.3)	5 (1.6) (0.5; 3.6)	3 (1.1) (0.2; 3.1)	7 (2.5) (1.0; 5.1)	-	-	-
	Related AEs	4 (2.9) (0.8; 7.3)	5 (1.6) (0.5; 3.6)	1 (0.4) (0.0; 2.0)	4 (1.4) (0.4; 3.7)	-	-	-
	Serious adverse events (SAEs)	4 (2.9) (0.8; 7.3)	4 (1.2) (0.3; 3.2)	6 (2.2) (0.8; 4.6)	8 (2.9) (1.3; 5.6)	-	-	-
	AEs leading to disc.	0 (0.0; 2.7)	1 (0.3) (0.0; 1.7)	0 (0.0; 1.3)	1 (0.4) (0.0; 2.0)	-	-	-

	GI Hemorrhage PTs							
	All AEs	6 (4.4) (1.6; 9.3)	9 (2.8) (1.3; 5.3)	9 (3.2) (1.5; 6.0)	18 (6.5) (3.9; 10.1)	-	-	-
	Grade 3/4 AEs	1 (0.7) (0.0; 4.0)	3 (0.9) (0.2; 2.7)	2 (0.7) (0.1; 2.6)	6 (2.2) (0.8; 4.7)	-	-	-
	Related AEs	2 (1.5) (0.2; 5.2)	4 (1.2) (0.3; 3.2)	1 (0.4) (0.0; 2.0)	3 (1.1) (0.2; 3.1)	-	-	-
	SAEs	1 (0.7) (0.0; 4.0)	2 (0.6) (0.1; 2.2)	4 (1.4) (0.4; 3.6)	5 (1.8) (0.6; 4.2)	-	-	-
	AEs leading to disc.	0 (0.0; 2.7)	0 (0.0; 1.1)	0 (0.0; 1.3)	0 (0.0; 1.3)	-	-	-
	CNS Hemorrhage PTs							
	All AEs	3 (2.2) (0.5; 6.3)	2 (0.6) (0.1; 2.2)	2 (0.7) (0.1; 2.6)	3 (1.1) (0.2; 3.1)	-	-	-
	Grade 3/4 AEs	3 (2.2) (0.5; 6.3)	2 (0.6) (0.1; 2.2)	1 (0.4) (0.0; 2.0)	1 (0.4) (0.0; 2.0)	-	-	-
	Related AEs	2 (1.5) (0.2; 5.2)	1 (0.3) (0.0; 1.7)	0 (0.0; 1.3)	1 (0.4) (0.0; 2.0)	-	-	-
	SAEs	3 (2.2) (0.5; 6.3)	2 (0.6) (0.1; 2.2)	2 (0.7) (0.1; 2.6)	3 (1.1) (0.2; 3.1)	-	-	-
	AEs leading to disc.	0 (0.0; 2.7)	1 (0.3) (0.0; 1.7)	0 (0.0; 1.3)	1 (0.4) (0.0; 2.0)	-	-	-

- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- Two-sided 95% CI is derived from the Pearson-Clopper formula.
MedDRA version 23.1 have been used for the reporting of AEs.
* A2203 patients received at least 5 years of treatment or discontinued early from the study and A2120 patients received minimum 12 cycles and up to 24 cycles of treatment.
** Patients have received at least 5 years of treatment or have discontinued early from the study
Source: [Annex 7-Table 1.5-1.1.2], [Annex 7-Table 1.5-1.1.2p], [Annex 7-Table 1.5-1.2.2], [Annex 7-Table 1.5-1.2.2p], [Annex 7-Table 1.5-1.3.2] and [Annex 7-Table 1.5-1.3.2p].

Table 8-3 Important identified risk of significant bleeding: other details

Name of the risk: Significant bleeding	Details
Potential mechanisms	In a subset of patients the potential mechanism might include thrombocytopenia.
Evidence source(s) and strength of evidence	The risk has been observed in preclinical and clinical studies. **Literature evidence:** **Incidence:** No information on the gastrointestinal hemorrhage incidence in untreated CML patients were identified from the literature. However, there is some information that the risk of bleeding is increased in cancer patients as compared with general population. GI hemorrhage: A cohort study in Italy found an incidence of 15.7 cases in 100 person years for major bleeding. The 12-month cumulative incidence of major bleeding was 12.4% with respect to cancer stage, incidence per 100 person-years was 42.8, 19.1 and 3.4 in patients with severe, moderately severe and less severe cancer, respectively. Overall cancer patients had 2.2 times more risk for major bleeding compared with patients without cancer (Prandoni et al 2002). Hutten et al (2000) analysed patients from two large clinical trials, and they found an incidence major bleeding of 13.3 per 100 patient-years in patients with malignancies as compared with 2.1 per 100 patient-years in patients without malignancies. The follow-up of patients with advanced haematological malignancies followed at home in Italy showed that 26% of those patients had significant episodes of bleeding, with a median number of 2 hemorrhages per patient (Cartoni et al 2009). **Prevalence:** Type of hematological and non-hematological AEs were studied among 250 chronic myeloid leukemia patients on imatinib. Out of 150 late chronic phase patients 8% had hemorrhages (13/150) while out of 100 early chronic phase patients 3% had hemorrhages (3/100) (Breccia et al 2008). Hemorrhaging occurs in approximately 6-10% of patients with advanced cancer. In some patients it may be the immediate cause of death (Pereira and Phan 2004). Bleeding may result from local vessel damage and invasion or from systemic processes such as disseminated intravascular coagulopathy or abnormalities in platelets. The underlying causes of these abnormalities are varied and include liver failure, medications such as anticoagulants, chemotherapy, radiotherapy surgery, and cancer itself (Dutcher 1987). CNS hemorrhage: In an autopsy study of patients with cancer, 14.6% had pathologic evidence of cerebrovascular disease (CVD), and in 7.4% clinical symptoms of CVD had been present in life. In patients with leukemia, hemorrhages (72.4%) were much more common than ischemic infarcts. In lymphoma patients, the incidence of cerebral bleeding was lower (36.3%). In both groups, the leading causes of ischemic infarction were septic thrombi and intravascular coagulation. In patients with carcinoma, cerebral infarctions (54.1%) were more frequent than hemorrhages (Graus et al 1985).

Name of the risk: Significant bleeding	**Details**
Characterization of the risk:	Significant bleeding group included anal haemorrhage, gastrointestinal, cerebral haemorrhage, haemorrhoidal haemorrhage, rectal haemorrhage, upper gastrointestinal haemorrhage, gastric occult blood positive, haematochezia, melaena, subdural hematoma, and subdural haemorrhage. At the time of 108-month cut-off, the frequency of significant bleeding was higher in the nilotinib 400 mg group (6.9%) than in the nilotinib 300 mg group (3.6%). Of these, 13 patients had SAEs (six patients in the nilotinib 300 mg group, and seven patients in the nilotinib 400 mg group). One case of rectal hemorrhage in the nilotinib 300 mg group, and one case each of hemorrhoidal hemorrhage, melena and rectal hemorrhage in the nilotinib 400 mg group were considered related to study drug and none led to study drug discontinuation (CAMN107A2303 108-month update clinical study report (CSR) Table 14.3.1-2.1). **GI Hemorrhage:** At the time of 108-month cut-off, 26 patients were reported with an AE grouped under GI hemorrhage: eight patients (2.9%) in the nilotinib 300 mg group, and 18 patients (6.5%) in the nilotinib 400 mg group. Grade 3/4 AEs were reported in, two patients (0.7%) in the nilotinib 300 mg group, and six patients (2.2%) in the nilotinib 400 mg group. Four patients had study drug-related AEs: one patient in the nilotinib 300 mg group (PT: rectal hemorrhage), and three patients in the nilotinib 400 mg group (PT: rectal hemorrhage, hemorrhoidal hemorrhage and melena). Gastrointestinal hemorrhage group included anal hemorrhage, GI hemorrhage, haemorrhoidal hemorrhage, rectal hemorrhage, gastric occult blood positive, haematochezia, melena, and upper gastrointestinal hemorrhage. **CNS Hemorrhage** At the time of 108-month cut-off, there were four patients who reported events of CNS hemorrhage: two patients (one event each of subdural hematoma and subdural hemorrhage) in the nilotinib 300 mg group. Two patients in the nilotinib 400 mg group who both had cerebral hemorrhage (Study CAMN107A2303 108-month update CSR Table 14.3.1-2.1). The CNS hemorrhage group included cerebral hemorrhage, subdural hematoma, and subdural hemorrhage. None of the pediatric patients experienced significant bleeding.
Risk factors and risk groups	Patients with thrombocytopenia.
Preventability	Unknown.
Impact on the benefit-risk balance of the product	Excessive bleeding and hemorrhage can lead to significant morbidity: complications from blood transfusions, dehydration secondary to hemorrhagic diarrhea and complications of CNS bleeding
Public health impact	Given the relatively low prevalence of CML in the overall population and the frequency of this risk, the potential public health impact is low.

8.3.1.2 Important identified risk: Severe infections

Table 8-4 Clinical trial data of severe infections

Risk	Severe Infection							
Frequency with 95% CI and Severity and nature of risk Seriousness/outcomes		CAMN107A2101		CAMN107A2303		CAMN107A2203 and CAMN107A2120* (Pediatric population)		
		LPLV**		LPLV		LPLV		
		Imatinib resistant/intolerant		Newly diagnosed		Imatinib/ dasatinib/ resistant/intolerant	Newly diagnosed	All patients
		CML-AP	CML-CP	CML-CP		Ph+ CML-CP		
		400 mg bid		300 mg bid	400 mg bid	230 mg/m^2 bid		
		N=137	N=321	N=279	N=277	N=44	N=25	N=69
	Severe infection	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)	n (%) (95% CI)
	All AEs	12 (8.8) (4.6; 14.8)	19 (5.9) (3.6; 9.1)	12 (4.3) (2.2; 7.4)	17 (6.1) (3.6; 9.6)	1 (2.3) (0.1, 12.0)	1 (4.0) (0.1, 20.4)	2 (2.9) (0.4, 10.1)
	Grade 3/4 AEs	10 (7.3) (3.6; 13.0)	10 (3.1) (1.5; 5.7)	5 (1.8) (0.6; 4.1)	11 (4.0) (2.0; 7.0)	0 (0.0, 8.0)	0 (0.0, 13.7)	0 (0.0, 5.2)
	Related AEs	4 (2.9) (0.8; 7.3)	3 (0.9) (0.2; 2.7)	0 (0.0; 1.3)	1 (0.4) (0.0; 2.0)	0 (0.0, 8.0)	0 (0.0, 13.7)	0 (0.0, 5.2)
	SAEs	10 (7.3) (3.6; 13.0)	7 (2.2) (0.9; 4.4)	6 (2.2) (0.8; 4.6)	9 (3.2) (1.5; 6.1)	0 (0.0, 8.0)	0 (0.0, 13.7)	0 (0.0, 5.2)
	AEs leading to disc.	2 (1.5) (0.2; 5.2)	1 (0.3) (0.0; 1.7)	0 (0.0; 1.3)	1 (0.4) (0.0; 2.0)	0 (0.0, 8.0)	0 (0.0, 13.7)	0 (0.0, 5.2)
	Sepsis PTs							
	All AEs	1 (0.7) (0.0; 4.0)	5 (1.6) (0.5; 3.6)	2 (0.7) (0.1; 2.6)	4 (1.4) (0.4; 3.7)	-	-	-
	Grade 3/4 AEs	1 (0.7) (0.0; 4.0)	5 (1.6) (0.5; 3.6)	2 (0.7) (0.1; 2.6)	4 (1.4) (0.4; 3.7)	-	-	-
	Related AEs	0	1 (0.3)	0	0	-	-	-

Risk	Severe Infection							
		(0.0; 2.7)	(0.0; 1.7)	(0.0; 1.3)	(0.0; 1.3)			
	SAEs	1 (0.7) (0.0; 4.0)	4 (1.2) (0.3; 3.2)	1 (0.4) [0.0; 2.0]	3 (1.1) (0.2; 3.1)	-	-	-
	AEs leading to disc.	1 (0.7) (0.0; 4.0)	0 (0.0; 1.1)	0 (0.0; 1.3)	1 (0.4) (0.0; 2.0)	-	-	-
	Pneumonia PTs							
	All AEs	11 (8.0) (4.1; 13.9)	14 (4.4) (2.4; 7.2)	12 (4.3) (2.2; 7.4)	14 (5.1) (2.8; 8.3)	1 (2.3) (0.1, 12.0)	1 (4.0) (0.1, 20.4)	2 (2.9) (0.4, 10.1]
	Grade 3/4 AEs	9 (6.6) (3.0; 12.1)	5 (1.6) (0.5; 3.6)	4 (1.4) (0.4; 3.6)	8 (2.9) (1.3; 5.6)	0 (0.0, 8.0)	0 (0.0, 13.7)	0 (0.0, 5.2)
	Related AEs	4 (2.9) (0.8; 7.3)	2 (0.6) (0.1; 2.2)	0 (0.0; 1.3)	1 (0.4) (0.0; 2.0)	0 (0.0, 8.0)	0 (0.0, 13.7)	0 (0.0, 5.2)
	SAEs	9 (6.6) (3.0; 12.1)	3 (0.9) (0.2; 2.7)	6 (2.2) (0.8; 4.6)	6 (2.2) (0.8; 4.7)	0 (0.0, 8.0)	0 (0.0, 13.7)	0 (0.0, 5.2)
	AEs leading to disc.	1 (0.7) (0.0; 4.0)	1 (0.3) (0.0; 1.7)	0 (0.0; 1.3)	0 (0.0; 1.3)	0 (0.0, 8.0)	0 (0.0, 13.7)	0 (0.0, 5.2)

- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- Two-sided 95% CI is derived from the Pearson-Clopper formula.
MedDRA version 23.1 have been used for the reporting of AEs.
* A2203 patients received at least 5 years of treatment or discontinued early from the study and A2120 patients received minimum 12 cycles and up to 24 cycles of treatment.
** Patients have received at least 5 years of treatment or have discontinued early from the study
Source: [Annex 7-Table 1.5-2.1.2], [Annex 7-Table 1.5-2.1.2p], [Annex 7-Table 1.5-2.2.2], [Annex 7-Table 1.5-2.2.2p], [Annex 7-Table 1.5-2.3.2] and [Annex 7-Table 1.5-2.3.2p].

Table 8-5 Important identified risk of severe infections: other details

Name of the risk: Severe infections	Details
Potential mechanisms	In a subset of patients the potential mechanism might include leukopenia.
Evidence source(s) and strength of evidence	The risk has been observed in preclinical and clinical studies. **Literature evidence:** **Incidence:** No information on the severe infections incidence in untreated CML patients could be identified from the literature. To evaluate temporal changes in the incidence and outcome of sepsis in the U.S. from 1979 through 2000, Martin et al (2003) used the National Hospital Discharge Survey. There were 10,319,418 reported cases of sepsis (accounting for 1.3% of all hospitalizations). The number of patients with sepsis per year increased from 164,072 in 1979 to 659,935 in 2000 (an increase of 13.7% per year). After normalization to the population distribution in the 2000 U.S. Census, the incidence of sepsis increased over the 22-year period from 82.7 cases per 100,000 population to 240.4 cases per 100,000 population, for an annualized increase of 8.7%. The increasing incidence was most apparent during the first two sub-periods, from 1979 through 1989. The average age of patients with sepsis increased consistently over time, from 57.4 years in the first sub-period to 60.8 years in the last sub-period. In Spain, the source of information was the Minimum Basic Hospital Data Set from the Region of Madrid in 2001 (Inigo et al 2006). Annual incidence was 14.1/10,000 inhabitants, being highest for those 84 and older (230.8/10,000). Mean age was 62.5 years; 59.7% were male and 1.7 infections per episode were detected. More frequently identified micro-organisms were *Streptococcus* sp., *Staphylococcus* sp., *Escherichia coli* and *Candida sp.* The most frequent organic dysfunctions were renal (39.7%) and respiratory (35.7%). **Prevalence:** A multi-center, retrospective study was conducted to assess epidemiology of bacteraemia and invasive fungal diseases (IFD) in children with AML. Proportion rate per 1,000 person-days at risk, and cumulative risk of bacteraemia and IFD in children with AML was assessed. The overall cumulative risk for bacteraemia was 51% (95% CI: 43–58) while for IFD it was 16% (95% CI: 12–21) (Castagnola et al 2010). A study was undertaken to assess the frequency of blood stream infections (BSIs) during neutropenia in different cycles of intensive chemotherapy treatment in AML. Overall BSI rate was found 13.2 per 1000 hospital days (Syrjälä et al 2010). Data for all 1999 hospitalizations from six states (Florida, Massachusetts, New Jersey, New York, Virginia, and Washington) were merged with US Census data, Centers for Disease Control vital statistics and National Cancer Institute, Surveillance, Epidemiology, and End Results initiative cancer prevalence data. There were 606,176 cancer hospitalizations identified, with severe sepsis present in 29,795 (4.9%). Projecting national estimates for the US population, cancer patients account for 126,209 severe sepsis cases annually, or 16.4 cases per 1000 people with cancer per year (Williams et al 2004).

Name of the risk: Severe infections	**Details**
Characterization of the risk:	Severe infections including sepsis and pneumonia are not uncommon in CML patients with compromised marrow function at baseline. Severe infections are well-recognized co-morbid conditions in an acutely ill population of leukemic patients, and infections may result from neutropenia. Not all patients experiencing severe infections during therapy with nilotinib were neutropenic. The AEs of sepsis and pneumonia were included as the indicators for Severe Infections. Overall, four patient (1.4%) in the nilotinib 400 mg bid group and two patients (0.7%) in the nilotinib 300 mg bid group experienced AEs grouped under sepsis. Three patients in nilotinib 400 mg bid group and one in the 300 mg group had SAEs. None of them were related to nilotinib. There was one patient in nilotinib 400 mg who discontinued due to sepsis. Overall, 12 patients (4.3%) in the nilotinib 300 mg bid group and 14 patients (5.1%) in the nilotinib 400 mg bid group experienced AEs grouped under pneumonia. Six patients in nilotinib 300 mg and 400 mg groups had SAEs. One patient in the 400 mg group with pneumonia had an AE related to nilotinib. None of them led to discontinuation. In nilotinib 400 mg group one patient died due to sepsis and in 300 mg nilotinib group, one patient died due to pneumonia, within 28 days of last treatment (CSR CAMN107A2303 108-month update). Pediatric population: One patient in the newly diagnosed group had pneumonia. None of the patients reported sepsis in either group. The safety profile in the pediatric population is consistent with the known safety profile of nilotinib in the adult population.
Risk factors and risk groups	Patients with decreased blood count.
Preventability	Unknown.
Impact on the benefit-risk balance of the product	Severe infections can lead to a decreased quality of life or be life threatening regardless of the fact that fatalities as a result of infections due to cancer treatments have decreased over the past decade
Public health impact	Given the relatively low prevalence of CML in the overall population and the frequency of this risk, the potential public health impact is low.

8.3.1.3 Important identified risk: Growth retardation

Table 8-6 Clinical trial data of growth retardation

Risk	Growth retardation			
Frequency with 95% CI and Severity and nature of risk Seriousness/outcomes		**CAMN107A2203 and CAMN107A2120* (Pediatric population)**		
		Imatinib/ dasatinib/ resistant/ intolerant	**Newly diagnosed**	**All patients**
		LPLV		
		Ph+ CML-CP		
		230 mg/m² bid		
		N=44	**N=25**	**N=69**
	Growth retardation	**n (%) (95% CI)**	**n (%) (95% CI)**	**n (%) (95% CI)**
	All AEs	2 (4.5) (0.6; 15.5)	1 (4.0) (0.1; 20.4)	3 (4.3) (0.9; 12.2)
	Grade 3/4 AEs	0 (0.0; 8.0)	0 (0.0; 13.7)	0 (0.0; 5.2)
	Related AEs	2 (4.5) (0.6; 15.5)	1 (4.0) (0.1; 20.4)	3 (4.3) (0.9; 12.2)
	SAEs	1 (2.3) (0.1; 12.0)	0 (0.0; 13.7)	1 (1.4) (0.0; 7.8)
	AEs leading to disc.	0 (0.0; 8.0)	0 (0.0; 13.7)	0 (0.0; 5.2)

- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- Two-sided 95% CI is derived from the Pearson-Clopper formula.
MedDRA version 23.1 have been used for the reporting of AEs.
* A2203 patients received at least 5 years of treatment or discontinued early from the study and A2120 patients received minimum 12 cycles and up to 24 cycles of treatment.
Source: [Annex 7-Table 1.5-3.1.2p].

Table 8-7 Important identified risk of growth retardation: other details

Growth retardation in children	Details
Potential mechanisms	Unknown
Evidence sources and strength of evidence	The risk has been observed in preclinical and clinical studies. **Literature evidence:** Data were collected retrospectively from a total of 81 children and adolescents (50 boys and 31 girls) with CML-CP who were identified in the French pediatric registry as treated with imatinib. Median age at the time of the start of imatinib was 11.5 years (range 10 months-17.5 years), including 10 patients between 16 and 17 years and 2 patients only at the age of 17 and thereafter. Median follow-up from the start of imatinib was 40 months (range: 1 to 110) and the median duration of imatinib treatment was 30 months (range: 1 to 110). Changes in body height were analyzed during the treatment with imatinib front line in patients with sufficient data and follow-up. Height was expressed as standard deviation score (SDS). Sixty-seven patients were assessable for paired analysis at the start of imatinib and 12 months later. The height SDS in this group of patients was significantly lower ($p<0.0001$) 12 months after the start of imatinib with a median variation of -0.32 SDS (range: -1.59 to + 0.23). Data available from 43 children were analyzed at - the start of imatinib, 12 months and 24 months later. It was observed that the height SDS in this group of patients was significantly lower 12 months and 24 months after the start of imatinib overall ($p<0.0001$) compared to the height SDS at the start of imatinib, indicating a statistically significant deceleration in growth during the first 2 years of imatinib treatment. The growth deceleration which was observed overall remains significant irrespective of sex and pubertal age. A significant decrease in the difference of the paired height SDS was observed in each subgroup 12 months after the start of imatinib. The height SDS in boys and girls was significantly ($p < 10^{-4}$) lower 12 months after the start of imatinib. No significant difference was observed with the height SDS at 12 months in patients who started imatinib at a pre-pubertal age or a post-pubertal age was compared overall and by gender (Millot et al 2014). Pediatric Ph+ ALL: No case reports of growth retardation in children were received for either of the studies – I2301 and AIT07. Incidence: No publications have been identified presenting the incidence specific for the unexposed target populations. Information on the frequency of growth retardation in untreated patients with CML and ALL patients is very scarce and sometimes contradictory. Berglund et al (1985) analyzed growth of 10 children with ALL diagnosed between 18 months and 7 years of age and found that the mean SDS for both height and weight decreased for at least one year before "the children showed any clinical symptoms which led to the diagnosis of leukemia". Berry et al (1983) analyzed 127 children with ALL and found that 80% of boys in <4 year age group had heights below the 50th percentile level for their age group at the time of initial diagnosis. However, other authors (Schriock et al 1991, Katz et al 1993, Vilela and Viana 2007) found that distribution of height at diagnosis of ALL was similar to reference populations. On the other hand, Halton et al (1995) conducted a prospective analysis of the bone and mineral status in 40 children with ALL and concluded that most

Growth retardation in children	Details
	children with ALL had alteration in bone metabolism and bone mass at the time of diagnosis implicating the leukemic process as causative. The negative effect of treatment on growth of children with ALL is well documented in the literature. The largest cohort of childhood ALL survivors evaluated for adult height was reported in 2007 (Chow et al 2007) from the Childhood Cancer Survival Study based in the US and Canada. The results were obtained from a cross-sectional study of 2434 ALL survivors and 3009 siblings. All survivor treatment exposure groups (chemotherapy alone, chemotherapy with cranial or craniospinal radiotherapy) had decreased adult height (height SDS < -2) compared with siblings (P< 0.001). Among survivors, significant risk factors for short stature included diagnosis of ALL before puberty, higher-dose cranial radiotherapy (=20 Gy versus < 20 Gy), any radiotherapy to the spine, and female sex. Growth deficiency in children treated for ALL has been reported also from other geographic regions: Vilela and Viana (2007) found height deficit at the end of the therapeutic treatment in 129 children analyzed from a total of 351 cases diagnosed between 1987 and 1994 in Brazil.
Characterization of the risk:	Novartis performed an interim 36-cycle analysis in Study CAMN107A2203, a multi-center, open label, non-controlled phase II study evaluating the efficacy and safety of oral nilotinib in pediatric patients with newly diagnosed Ph+ CML-CP or with Ph+ CML-CP/AP resistant or intolerant to either imatinib or dasatinib. In Study CAMN107A2203, a signal of trend towards deceleration was identified at 36-cycle analysis and confirmed at 48-cycle analysis. This is further supported by the long-term analysis at 66-cycles. The final report for Study CAMN107A2203 _hd2_Annex_2___Tabulated_su173024presented the final efficacy and safety results of nilotinib (last patient last visit occurred on 28-Aug-2020), when all patients had completed 66 Cycles each of 28 days, or discontinued early. The most frequent AEs reported were headache, increased blood bilirubin, pyrexia, ALT increased, nausea, and rash. AEs were adequately managed through monitoring and dose modifications (CSR Study CAMN107A2203). The analysis of the data on growth and development allowed confirming the trend towards growth deceleration; no trend was observed on weight, bone age, bone biomarkers or sexual maturation (Tanner stage). The trend observed on growth deceleration was considered as medically relevant. The differences on loss of height SDS according to age (< 12 and ≥ 12 years old) and the potential effect of puberty inducing a catch up of growth were inconclusive (CSR Study CAMN107A2203). No new or other safety signals were observed with nilotinib treatment in pediatric population resistant or intolerant to either imatinib or dasatinib and newly diagnosed after the 48-cycle. The term 'Growth retardation' was incorporated in the ADR table and information was added in Section 6 'Warnings and Precautions' and Section 7 'Adverse drug reactions' of the core data sheet and the Tasigna national prescribing information.
Risk factors and risk groups	Especially pre-pubertal age group.

Growth retardation in children	Details
Preventability	Periodic monitoring of growth should be performed in children who have not achieved their adult height.
Impact on the benefit-risk balance of the product	Low to moderate within the pediatric population.
Public health impact	Unknown, potentially significant within the pediatric population.

8.3.1.4 Important potential risk: Reproductive toxicity/pregnancy

Table 8-8 Clinical trial data of reproductive toxicity/pregnancy

Risk	**Reproductive toxicity/pregnancy**							
Frequency with 95% CI and Severity and nature of risk Seriousness/outcomes		**CAMN107A2101**		**CAMN107A2303**		**CAMN107A2203 and CAMN107A2120* (Pediatric population)**		
		Imatinib resistant/intolerant		**Newly diagnosed**		**Imatinib/ dasatinib/ resistant/intolerant**	**Newly diagnosed**	**All patients**
		LPLV**		**LPLV**		**LPLV**		
		CML-AP	**CML-CP**	**CML-CP**		**Ph+ CML-CP**		
		400 mg bid		**300 mg bid**	**400 mg bid**	**230 mg/m² bid**		
		N=137	**N=321**	**N=279**	**N=277**	**N=44**	**N=25**	**N=69**
	Reproductive toxicity/pregnancy	**n (%) (95% CI)**	**n (%) (95% CI)**	**n (%) (95% CI)**	**n (%) (95% CI)**	**n (%) (95% CI)**	**n (%) (95% CI)**	**n (%) (95% CI)**
	All AEs	3 (2.2) (0.5; 6.3)	2 (0.6) (0.1; 2.2)	3 (1.1) (0.2; 3.1)	10 (3.6) (1.7; 6.5)	1 (2.3) (0.1; 12.0)	3 (12.0) (2.5; 31.2)	4 (5.8) (1.6; 14.2)
	Grade 3/4 AEs	1 (0.7) (0.0; 4.0)	0 (0.0; 1.1)	1 (0.4) (0.0; 2.0)	1 (0.4) (0.0; 2.0)	0 (0.0; 8.0)	0 (0.0; 13.7)	0 (0.0; 5.2)
	Related AEs	2 (1.5) (0.2; 5.2)	0 (0.0; 1.1)	1 (0.4) (0.0; 2.0)	1 (0.4) (0.0; 2.0)	0 (0.0; 8.0)	0 (0.0; 13.7)	0 (0.0; 5.2)
	SAEs	1 (0.7) (0.0; 4.0)	0 (0.0; 1.1)	1 (0.4) (0.0; 2.0)	0 (0.0; 1.3)	0 (0.0; 8.0)	0 (0.0; 13.7)	0 (0.0; 5.2)
	AEs leading to disc.	1 (0.7) (0.0; 4.0)	0 (0.0; 1.1)	0 (0.0; 1.3)	0 (0.0; 1.3)	0 (0.0; 8.0)	0 (0.0; 13.7)	0 (0.0; 5.2)

- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- Two-sided 95% CI is derived from the Pearson-Clopper formula.

MedDRA version 23.1 have been used for the reporting of AEs.

* A2203 patients received at least 5 years of treatment or discontinued early from the study and A2120 patients received minimum 12 cycles and up to 24 cycles of treatment.

** Patients have received at least 5 years of treatment or have discontinued early from the study

Source: [Annex 7-Table 1.5-4.1.2] and [Annex 7-Table 1.5-4.1.2p].

Table 8-9 Clinical trial data of reproductive toxicity/pregnancy – Fetal outcomes in pregnancies with fetal outcome reported

Parameter	Detailed information
Frequency	**Fetal outcomes in pregnancies with fetal outcome reported**

	Exposure via father		Exposure via mother		All pregnancies with fetal outcome reported	
Pregnancy outcome	**n**	**%**	**n**	**%**	**n**	**%**
Normal infant	81	(94.2%)	144	(76.6%)	**225**	(82.1%)
Congenital anomaly major	-	-	5	(2.7%)	**5**	(1.8%)
Congenital anomaly minor	-	-	4	(2.1%)	**4**	(1.5%)
Congenital anomaly not otherwise specified (structural)	2	(2.3%)	4	(2.1%)	**6**	(2.2%)
Perinatal complication (non-structural)	1	-	4	(2.1%)	**5**	(1.8%)
Post-perinatal complication (non-structural)	1	(1.2%)	1	(0.5%)	**2**	(0.7%)
Abnormality, other (non-structural)	1	(1.2%)	2	(1.1%)	**3**	(1.1%)
Fetal death/ intrauterine death	-	-	21	(11.2%)	**21**	(7.7%)
Blighted ovum	-	-	1	(0.5%)	**1**	(0.4%)
Ectopic pregnancy	-	-	2	(1.1%)	**2**	(0.7%)
Total	**86**	**(100.0%)**	**188**	(100.0%)	**274**	**(100.0%)**

Birth types reported in pregnancies

Parameter	Detailed information						
		Exposure via father		Exposure via mother		All pregnancies with birth type reported	
	Birth type	**n**	**%**	**n**	**%**	**n**	**%**
	Full-term live birth	86	76.1%	158	57.0%	**244**	62.6%
	Premature live birth	9	7.9%	15	5.4%	**24**	6.2%
	Post-mature live birth	2	1.8	1	0.4%	**3**	0.8%
	Elective termination	8	7.1%	33	11.9%	**41**	10.5%
	Therapeutic abortion	1	0.9%	19	6.9%	**20**	5.1%
	Intrauterine death	-	-	1	0.4%	**1**	0.3%
	Stillbirth	-	-	6	2.2%	**6**	1.5%
	Spontaneous abortion/ miscarriage	7	6.2%	34	12.3%	**41**	10.5%
	Abortion not otherwise specified	-	-	10	3.6%	**10**	2.6%
	Total	**113**	100.00%	**277**	100.00%	**390**	100.00%
Source: PSUR (DLP 31-Jan-2020)							

Table 8-10 Important potential risk of reproductive toxicity/pregnancy: other details

Name of the risk Reproductive toxicity/pregnancy	**Details**
Potential mechanisms	Unknown
Evidence source(s) and strength of evidence	The risk has been observed in preclinical and clinical studies. **Literature evidence:** Epidemiologic data regarding pregnancy outcomes are not available on untreated patients with CML. Most of the published data on the prevalence of various pregnancy outcomes are from patients treated with imatinib. Among men, an early report of Novartis data described 13 pregnancies in the partners of men who were taking imatinib at conception. The outcome was known for only 8 of these; 3 ended in abortion (two therapeutic and one spontaneous), one *in utero* death occurred at 13 weeks, and four normal pregnancies resulted in four normal infants. In contrast, a later report from M.D. Anderson noted seven normal pregnancies and one spontaneous abortion in the partners of eight men treated with imatinib for a median of 20 months. One infant was born with a malrotation of the gastrointestinal tract, which required surgical correction. Subsequently, 10 additional uneventful pregnancies were reported in the partners of 9 men on both standard and high doses of imatinib (Apperley 2009). Among women, Ault et al (2006) reported their experience on 10 women who conceived while receiving treatment for imatinib, all of whom discontinued therapy on recognition of pregnancy. Two had spontaneous abortions, one had an elective abortion. All the other pregnancies were uneventful. One infant was noted to have hypospadias. Subsequently, Pye et al (2008) reported pregnancy outcomes data on 125 (69%) of 180 women exposed to imatinib during pregnancy. Among women with known outcomes, 50% delivered normal infants and 28% underwent elective terminations (3 patients following the identification of abnormalities). Abnormalities were identified in 12 infants, 3 of whom had strikingly similar complex malformations (exomphalos and vertebral abnormalities (scoliosis/hemivertebrae) with or without abnormalities of the kidney (absent right kidney or right renal agenesis, duplex left kidney), hypoplastic lungs and shoulder anomaly). Eighteen pregnancies (14.4% of pregnancies with known outcomes) ended in spontaneous abortion (Pye et al 2008, Apperley 2009). In the general population, according to the CDC (2008), the overall prevalence of major defects was 3.0 per 100 in 2005 in the Metropolitan Atlanta Congenital Defects Program (MACDP). This program monitors the prevalence of all major structural or genetic defects at the time of delivery among live births, stillbirths, and pregnancies electively terminated after prenatal diagnosis of defects at ≥20 weeks' gestation in the five central counties of metropolitan Atlanta. MACDP defines major structural or genetic birth defects as conditions that 1) result from a malformation, deformation, or disruption in one or more parts of the body, a chromosomal abnormality, or a known clinical syndrome; 2) are present at birth; and 3) have a serious, adverse effect on health, development, or functional ability.

Name of the risk Reproductive toxicity/pregnancy	**Details**
	The European Surveillance of Congenital Anomalies (EUROCAT) is a European network of population-based registries for the epidemiologic surveillance of congenital anomalies that was started in 1979 and has surveyed more than 1.7 million births surveyed per year in Europe. It includes data from 43 registries in 23 countries and covers 29% of the European birth population. EUROCAT reported that the prevalence of all anomalies was 2.56 (95% CI: 2.55-2.58) per 100 births (live births , fetal deaths/still births from 20 weeks gestation and termination of pregnancy for fetal anomaly following prenatal diagnosis) (EUROCAT 2014). In the general population, spontaneous abortion is the most common complication of early pregnancy, its frequency decreasing with increasing gestational age. Eight to 20 percent of clinically recognized pregnancies at less than 20 weeks of gestation undergo spontaneous abortion with 80% of these occurring in the first 12 weeks of gestation. The overall risk of spontaneous abortion after 15 weeks is low (about 0.6%) for chromosomally and structurally normal fetuses, but varies with the presence of associated risk factors. Loss of unrecognized or subclinical pregnancies occurs in 13 to 26% of all pregnancies. If pre-implantation losses are considered, approximately 50% of fertilized oocytes do not result in a live birth (Tulandi and Al-Fozan 2013).
Characterization of the risk:	There is limited amount of data from the use of nilotinib in pregnant women. Studies in animals have shown reproductive toxicity. In preclinical studies nilotinib did not induce teratogenicity, but did show embryo- and fetotoxicity at doses that also showed maternal toxicity. Increased post-implantation loss was observed in both the fertility study, which involved treatment of both males and females, and the embryo toxicity study, which involved treatment of females. Embryo-lethality and foetal effects (mainly decreased fetal weights, premature fusion of the facial bones (fused maxilla/zygomatic) visceral and skeletal variations) in rats and increased resorption of fetuses and skeletal variations in rabbits were present in the embryo toxicity studies. In a pre- and post-natal development study in rats, maternal exposure to nilotinib caused reduced pup body weight with associated changes in physical development parameters as well as reduced mating and fertility indices in the offspring. Exposure to nilotinib in females at No-Observed-Adverse-Effect-Levels was generally less or equal to that in humans at 800 mg/day. No effects on sperm count/motility or on fertility were noted in male and female rats up to the highest tested dose, approximately five-times the recommended dosage for humans.
Risk factors and risk groups	Female patients of reproductive age.
Preventability	Tasigna should not be used during pregnancy unless necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the fetus. Women of childbearing potential must be advised to use highly effective method of contraception while receiving Tasigna and for up to 2 weeks after ending treatment.
Impact on the benefit-risk balance of the product	The evaluation of this potential risk revealed no evidence to support a causal relationship between the events within the scope of any of those

Name of the risk Reproductive toxicity/pregnancy	**Details**
	risks and the exposure to nilotinib. The risk is properly communicated through the current labeling.
Public health impact	Given the relatively low prevalence of CML in the overall population and the frequency of this risk, the potential public health impact is low.

8.3.1.5 Important potential risk: Skin malignancy

Table 8-11 Clinical trial data of Skin malignancy

Risk	**Skin malignancy**							
Frequency with 95% CI and Severity and nature of risk Seriousness/outcomes		**CAMN107A2101**		**CAMN107A2303**		**CAMN107A2203 and CAMN107A2120* (Pediatric population)**		
		LPLV**		**LPLV**		**LPLV**		
		Imatinib resistant/intolerant		**Newly diagnosed**		**Imatinib/ dasatinib/ resistant/intolerant**	**Newly diagnosed**	**All patients**
		CML-AP	**CML-CP**	**CML-CP**		**Ph+ CML-CP**		
		400 mg bid		**300 mg bid**	**400 mg bid**	**230 mg/m² bid**		
		N=137	**N=321**	**N=279**	**N=277**	**N=44**	**N=25**	**N=69**
	Skin malignancy	**n (%) (95% CI)**	**n (%) (95% CI)**	**n (%) (95% CI)**	**n (%) (95% CI)**	**n (%) (95% CI)**	**n (%) (95% CI)**	**n (%) (95% CI)**
	All AEs	2 (1.5) (0.2; 5.2)	5 (1.6) (0.5; 3.6)	14 (5.0) (2.8; 8.3)	7 (2.5) (1.0; 5.1)	-	-	-
	Grade 3/4 AEs	2 (1.5) (0.2; 5.2)	3 (0.9) (0.2; 2.7)	4 (1.4) (0.4; 3.6)	2 (0.7) (0.1; 2.6)	-	-	-
	Related AEs	0 (0.0; 2.7)	0 (0.0; 1.1)	2 (0.7) (0.1; 2.6)	0 (0.0; 1.3)	-	-	-
	SAEs	2 (1.5) (0.2; 5.2)	3 (0.9) (0.2; 2.7)	7 (2.5) (1.0; 5.1)	2 (0.7) (0.1; 2.6)	-	-	-
	AEs leading to disc.	1 (0.7) (0.0; 4.0)	0 (0.0; 1.1)	1 (0.4) (0.0; 2.0)	0 (0.0; 1.3)	-	-	-

- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- Two-sided 95% CI is derived from the Pearson-Clopper formula.
MedDRA version 23.1 have been used for the reporting of AEs.
* A2203 patients received at least 5 years of treatment or discontinued early from the study and A2120 patients received minimum 12 cycles and up to 24 cycles of treatment.
** Patients have received at least 5 years of treatment or have discontinued early from the study
Source: [Annex 7-Table 1.5-5.1.2] and [Annex 7-Table 1.5-5.1.2p].

Table 8-12 Important potential risk of skin malignancy: other details

Name of the risk Skin malignancy	Details
Potential mechanisms	Unknown.
Evidence source(s) and strength of evidence	The risk has been observed in preclinical and clinical studies. **Literature evidence:** Based on SEER data for the period 1973-2000, the incidence of melanoma of the skin in the US was not statistically significantly higher in patients with CML when compared with the general population (standardized incidence ratio (SIR): 1.03, p>0.05; incidence rate (IR): 28.7 cases per 100,000 patient-years) (Ishibe and Curtis 2006). In a population-based study by Rebora et al (2010) that included CML patients from the Swedish Cancer Registry diagnosed between 1970 and 1995, the SIR showed a higher risk of melanoma, although again it was not statistically significantly higher compared with the general population (SIR: 1.40, 95% CI: 0.29 4.09; IR: 33.0 cases per 100,000 patient-years). In the case of other skin malignancies, including squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), the risk was higher in CML patients compared with the general population (SIR: 5.36, 95% CI: 3.18-8.47; IR: 197.9 cases per 100,000 patient-years) (Rebora et al 2010). At a US hospital, among 1,342 patients with CML treated between 1998 and 2010, 14 cases of non-melanoma skin cancer (NMSC) (BCC or SCC) were observed after a median of 107 months of follow-up (Verma et al 2011).
Characterization of the risk:	As a part of the non-clinical safety profiling of nilotinib in accordance to ICH guideline, a carcinogenicity study in mice (Study #1270142) was initiated in Sep-2013 after a 2-year carcinogenicity study was found negative for nilotinib being tumorigenic in rats (Study #0670450) in 2011. Study #1270142 is a 26-week carcinogenicity and toxicokinetic study with AMN107 in the transgenic rasH2 mice. Nilotinib was administered at dose levels of 0, 30, 100, or 300 mg/kg/day. On 04-Nov-2014, assessment of the preliminary histology results showed that there was evidence of a carcinogenic effect of nilotinib in the skin of mice. Squamous cell carcinoma in one mouse and benign squamous cell papilloma of the skin in 10 of a total of 50 mice (both sexes included) were detected in mice treated at 300 mg/kg/day (approximately 30 to 40 times the steady-state human daily exposure based on AUC). It also should be noted that moderate or marked epidermal hyperplasia was observed in the skin/subcutis of the distal tail in one male and one female given 100 mg/kg/day, representing approximately 10 to 20 times the human daily exposure. Nilotinib was not mutagenic, clastogenic or aneugenic in any of the *in vitro* or *in vivo* studies performed. Previous toxicity studies in mice up to 13 weeks, in rats up to 26 weeks, in dogs up to 4 weeks, and in Cynomolgus monkeys up to 39 weeks did not show any histological findings in the skin. Based on routine pharmacovigilance activities to date and the cumulative skin malignancy case review in Novartis safety database (ARGUS), there is no evidence suggesting a potential safety signal of skin malignancy associated with nilotinib treated patients. Pediatric population: None of the patients reported skin malignancy.
Risk factors and risk groups	The risk has been observed in preclinical and clinical studies. Having a personal history of NMSC, including BCC or SCC, is an independent risk

Name of the risk Skin malignancy	Details
	factor for the development of secondary cancers (Chen et al 2008, Wheless et al 2010). Evidence from the literature also suggests that NMSC at earlier age is associated with a higher risk of developing a secondary cancer. NMSC was associated with a statistically significantly increased risk in all age groups, but the relative risks were strongest in the younger age groups (Chen et al 2008).
Preventability	Unknown.
Impact on the benefit-risk balance of the product	The evaluation of this potential risk revealed no evidence to support a causal relationship between the events within the scope of any of those risks and the exposure to nilotinib. The risk is properly communicated through the current labeling.
Public health impact	A safety review of events of skin malignancy taking into consideration risk factors indicated that at the present time, there is a low incidence of skin malignancy events reported for Tasigna and no evidence of a positive association. Regarding squamous cell carcinoma of the skin, no clear signal has arisen from the analysis of safety information available to date and no clear association with Tasigna has been made. The clinical relevance of the preclinical findings is unclear and must be seen in the context of the prognosis of the primary disease.

8.3.2 SVII.3.2. Presentation of the missing information

Table 8-13 Missing information: Pediatric patients below 2 years of age

Name of missing information - Pediatric patients below 2 years of age	Details
Evidence source	Population in need of further characterization: There is limited experience with the use of nilotinib in pediatric patients <2 years old. There are currently no clinical trials in this population, however, Novartis will continue to perform routine pharmacovigilance and risk minimization activities in this group of pediatric patients below 2-years of age and continue monitoring cases reported to the safety database.

9 Part II Safety specification Module SVIII: Summary of the safety concerns

Table 9-1 Table Part II SVIII.1: Summary of safety concerns

Important identified risks	Significant bleeding Severe infections Growth retardation
Important potential risks	Reproductive toxicity/pregnancy Skin malignancy
Missing information	Pediatric patients below 2 years of age

10 Part III: Pharmacovigilance plan (including post-authorization safety studies)

10.1 Part III.1. Routine pharmacovigilance activities

10.1.1 Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up checklists:

Specific AE follow-up checklists will be used to collect further data to help further characterize and/or closely monitor each of the respective safety concerns specified below:

- Significant bleeding
- Severe infections
- Reproductive toxicity/pregnancy.

These checklists are provided in Annex 4 of the RMP.

Other forms of routine pharmacovigilance activities

Not applicable.

10.2 Part III.2. Additional pharmacovigilance activities

Not applicable.

10.3 Part III.3 Summary Table of additional pharmacovigilance activities

Table 10-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None.				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None.				

11 Part IV: Plans for post-authorization efficacy studies

Not applicable.

12 Part V: Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)

12.1 Part V.1. Routine risk minimization measures

Table 12-1 Table Part V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Important identified risks	
Significant bleeding.	**Routine risk communication:** SmPC Section 4.8 Package leaflet (PL) Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 SmPC Section 4.4 PL Section 1 **Other routine risk minimization measures beyond the Product Information:** None.
Severe infections.	**Routine risk communication:** SmPC Section 4.8 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimization measures beyond the Product Information**: None.
Growth retardation.	**Routine risk communication:** SmPC Section 4.4 SmPC Section 4.8 PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** Close monitoring of growth in pediatric patients is recommended in SmPC Section 4.4 and PL Section 2. **Other routine risk minimization measures beyond the Product Information:** None.
Important potential risks	
Reproductive toxicity/pregnancy.	**Routine risk communication:** SmPC Section 4.6 SmPC Section 4.8 SmPC Section 5.3 PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:**

Safety concern	Routine risk minimization activities
	SmPC Section 4.6 and PL Section 2 recommend usage of highly effective contraception and also that nilotinib should not be used during pregnancy unless it is highly required. **Other routine risk minimization measures beyond the Product Information:** None.
Skin malignancy.	**Routine risk communication** SmPC Section 5.3 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimization measures beyond the Product Information:** None.
Missing information	
Pediatric patients below 2 years of age.	**Routine risk communication** SmPC Section 4.2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimization measures beyond the Product Information:** None.

12.2 Part V.2. Additional Risk minimization measures

There are no additional risk minimization measures since routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

12.3 Part V.3 Summary of risk minimization measures

Table 12-2 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Significant bleeding	**Routine risk minimization measures:** SmPC Section 4.8 PL Section 4 **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up checklist for adverse reaction **Additional pharmacovigilance activities:** None
Severe infections	**Routine risk minimization measures:** SmPC Section 4.8 **Additional risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	None.	Targeted follow-up checklist for adverse reaction **Additional pharmacovigilance activities:** None
Growth retardation	**Routine risk minimization measures:** SmPC Section 4.8 Close monitoring of growth in pediatric patients is recommended in SmPC Section 4.4 and PL Section 2. **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None.
Important potential risks		
Reproductive toxicity/pregnancy	**Routine risk minimization measures:** SmPC Section 4.8 SmPC Section 5.3 SmPC Section 4.6 and PL Section 2 recommend usage of highly effective contraception and also that nilotinib should not be used during pregnancy unless it is highly required. **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up checklist for adverse reaction **Additional pharmacovigilance activities:** None
Skin malignancy	**Routine risk minimization measures:** SmPC Section 5.3 **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Missing information		
Pediatric patients below 2 years of age	**Routine risk minimization measures:** SmPC Section 4.2 **Additional risk minimization measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

13 Part VI: Summary of the risk management plan for Tasigna

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

The Tasigna Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Tasigna should be used.

This summary of the RMP for Tasigna 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 Tasigna's RMP.

13.1 Part VI: I. The medicine and what it is used for

Tasigna is authorized for:

- Treatment of adult and pediatric patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase (CP)
- Treatment of adult patients with chronic phase and accelerated phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib. Efficacy data in patients with CML in blast crisis (BC) are not available
- Treatment of pediatric patients with chronic phase Philadelphia chromosome positive CML with resistance or intolerance to prior therapy including imatinib.

It contains nilotinib as the active substance and it is given by hard capsules of 50 mg, 150 mg and 200 mg.

Further information about the evaluation of Tasigna's benefits can be found in Tasigna's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/tasigna.

13.2 Part VI: II. Risks associated with the medicine and activities to minimize or further characterize the risks

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

Measures to minimize 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 (e.g. with or without prescription) can help to minimize its risks.

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

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 Tasigna is not yet available, it is listed under 'missing information' below.

13.2.1 Part VI – II.A: List of important risks and missing information

Important risks of Tasigna are risks that need special risk management activities to further investigate or minimize 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 Tasigna. 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 (e.g. on the long-term use of the medicine).

Table 13-1 List of important risks and missing information

Important identified risks	Significant bleeding Severe infections Growth retardation
Important potential risks	Reproductive toxicity/pregnancy Skin malignancy
Missing information	Pediatric patients below 2 years of age

13.2.2 Part VI - II B: Summary of important risks

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

Table 13-2 Important identified risk Significant bleeding

Evidence for linking the risk to the medicine	This risk has been observed in preclinical and clinical studies. **Literature evidence:** **Incidence**: No information on the gastrointestinal hemorrhage incidence in untreated CML patients were identified from the literature. However, there is some information that the risk of bleeding is increased in cancer patients as compared with general population. GI hemorrhage: A cohort study in Italy found an incidence of 15.7 cases in 100 person years for major bleeding. The 12-month cumulative incidence of major bleeding was 12.4% with respect to cancer stage, incidence per 100 person-years was 42.8, 19.1 and 3.4 in patients with severe, moderately severe and less severe cancer, respectively. Overall cancer patients had 2.2 times more risk for major bleeding compared with patients without cancer (Prandoni et al 2002). Hutten et al (2000) analysed patients from two large clinical trials, and they found an incidence major bleeding of 13.3 per 100 patient-years

	in patients with malignancies as compared with 2.1 per 100 patient-years in patients without malignancies. The follow-up of patients with advanced haematological malignancies followed at home in Italy showed that 26% of those patients had significant episodes of bleeding, with a median number of 2 hemorrhages per patient (Cartoni et al 2009). **Prevalence**: Type of hematological and non-hematological AEs were studied among 250 chronic myeloid leukemia patients on imatinib. Out of 150 late chronic phase patients 8% had hemorrhages (13/150) while out of 100 early chronic phase patients 3% had hemorrhages (3/100) (Breccia et al 2008). Hemorrhages occur in approximately 6-10% of patients with advanced cancer. In some patients it may be the immediate cause of death (Pereira and Phan 2004). Bleeding may result from local vessel damage and invasion or from systemic processes such as disseminated intravascular coagulopathy or abnormalities in platelets. The underlying causes of these abnormalities are varied and include liver failure, medications such as anticoagulants, chemotherapy, radiotherapy surgery, and cancer itself (Dutcher 1987). CNS hemorrhage: In an autopsy study of patients with cancer, 14.6% had pathologic evidence of cerebrovascular disease (CVD), and in 7.4% clinical symptoms of CVD had been present in life. In patients with leukemia, hemorrhages (72.4%) were much more common than ischemic infarcts. In lymphoma patients, the incidence of cerebral bleeding was lower (36.3%). In both groups, the leading causes of ischemic infarction were septic thrombi and intravascular coagulation. In patients with carcinoma, cerebral infarctions (54.1%) were more frequent than hemorrhages (Graus et al 1985).
Risk factors and risk groups	Patients with thrombocytopenia.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 PL Section 4 **Additional risk minimization measures:** None.

Table 13-3 Important identified risk Severe infections

Evidence for linking the risk to the medicine	This risk has been observed in preclinical and clinical studies. **Literature evidence:** **Incidence**: No information on the severe infections incidence in untreated CML patients could be identified from the literature. To evaluate temporal changes in the incidence and outcome of sepsis in the U.S. from 1979 through 2000, Martin et al (2003) used the National Hospital Discharge Survey. There were 10,319,418 reported cases of sepsis (accounting for 1.3% of all hospitalizations). The number of patients with sepsis per year increased from 164,072 in 1979 to 659,935 in 2000 (an increase of 13.7% per year). After normalization to the population distribution in the 2000 U.S. Census, the incidence of sepsis increased over the 22-year period from 82.7 cases per 100,000 population to 240.4 cases

	per 100,000 population, for an annualized increase of 8.7%. The increasing incidence was most apparent during the first two sub-periods, from 1979 through 1989. The average age of patients with sepsis increased consistently over time, from 57.4 years in the first sub-period to 60.8 years in the last sub-period. In Spain, the source of information was the Minimum Basic Hospital Data Set from the Region of Madrid in 2001 (Inigo et al 2006). Annual incidence was 14.1/10,000 inhabitants, being highest for those 84 and older (230.8/10,000). Mean age was 62.5 years; 59.7% were male and 1.7 infections per episode were detected. More frequently identified micro-organisms were Streptococcus sp., Staphylococcus sp., Escherichia coli and Candida sp. The most frequent organic dysfunctions were renal (39.7%) and respiratory (35.7%). **Prevalence**: A multi-center, retrospective study was conducted to assess epidemiology of bacteraemia and IFD in children with AML. Proportion rate per 1,000 person-days at risk, and cumulative risk of bacteraemia and IFD in children with AML was assessed. The overall cumulative risk for bacteraemia was 51% (95% CI: 43–58) while for IFD it was 16% (95% CI: 12–21) (Castagnola et al 2010). A study was undertaken to assess the frequency of BSIs during neutropenia in different cycles of intensive chemotherapy treatment in AML. Overall BSI rate was found 13.2 per 1000 hospital days (Syrjälä et al 2010). Data for all 1999 hospitalizations from six states (Florida, Massachusetts, New Jersey, New York, Virginia, and Washington) were merged with US Census data, Centers for Disease Control vital statistics and National Cancer Institute, Surveillance, Epidemiology, and End Results initiative cancer prevalence data. There were 606,176 cancer hospitalizations identified, with severe sepsis present in 29,795 (4.9%). Projecting national estimates for the US population, cancer patients account for 126209 severe sepsis cases annually, or 16.4 cases per 1000 people with cancer per year (Williams et al 2004).
Risk factors and risk groups	Patients with decreased WBC count.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 **Additional risk minimization measures:** None.

Table 13-4 Important identified risk Growth retardation

Evidence for linking the risk to the medicine	This risk has been observed in preclinical and clinical studies. **Literature evidence:** Data were collected retrospectively from a total of 81 children and adolescents (50 boys and 31 girls) with CML-CP who were identified in the French pediatric registry as treated with imatinib. Median age at the time of the start of imatinib was 11.5 years (range 10 months-17.5 years), including 10 patients between 16 and 17 years and 2 patients only at the age of 17 and thereafter. Median follow-up from the start of imatinib was 40 months (range: 1 to 110) and the median duration of imatinib treatment was 30 months (range: 1 to 110).

Changes in body height were analyzed during the treatment with imatinib front line in patients with sufficient data and follow-up. Height was expressed as SDS. Sixty-seven patients were assessable for paired analysis at the start of imatinib and 12 months later. The height SDS in this group of patients was significantly lower ($p<0.0001$) 12 months after the start of imatinib with a median variation of -0.32 SDS (range: -1.59 to + 0.23).

Data available from 43 children were analyzed at - the start of imatinib, 12 months and 24 months later. It was observed that the height SDS in this group of patients was significantly lower 12 months and 24 months after the start of imatinib overall ($p<0.0001$) compared to the height SDS at the start of imatinib, indicating a statistically significant deceleration in growth during the first 2 years of imatinib treatment. The growth deceleration which was observed overall remains significant irrespective of sex and pubertal age. A significant decrease in the difference of the paired height SDS was observed in each subgroup 12 months after the start of imatinib. The height SDS in boys and girls was significantly ($p < 10^{-4}$) lower 12 months after the start of imatinib. No significant difference was observed with the height SDS at 12 months in patients who started imatinib at a pre-pubertal age or a post-pubertal age was compared overall and by gender. (Millot et al 2014).

Pediatric Ph+ ALL: No case reports of growth retardation in children were received for either of the studies – I2301 and AIT07.

Incidence: No publications have been identified presenting the incidence specific for the unexposed target populations.

Information on the frequency of growth retardation in untreated patients with CML and ALL patients is very scarce and sometimes contradictory.

Berglund et al (1985) analyzed growth of 10 children with ALL diagnosed between 18 months and 7 years of age and found that the mean SDS for both height and weight decreased for at least one year before "the children showed any clinical symptoms which led to the diagnosis of leukemia".

Berry et al (1983) analyzed 127 children with ALL and found that 80% of boys in <4 year age group had heights below the 50th percentile level for their age group at the time of initial diagnosis.

However, other authors (Katz et al 1993, Schriock et al 1991, Vilela and Viana 2007) found that distribution of height at diagnosis of ALL was similar to reference populations.

On the other hand, Halton et al (1995) conducted a prospective analysis of the bone and mineral status in 40 children with ALL and concluded that most children with ALL had alteration in bone metabolism and bone mass at the time of diagnosis implicating the leukemic process as causative.

The negative effect of treatment on growth of children with ALL is well documented in the literature. The largest cohort of childhood ALL survivors evaluated for adult height was reported in 2007 (Chow et al 2007) from the Childhood Cancer Survival Study based in the US and Canada. The results were obtained from a cross-sectional study of 2434 ALL survivors and 3009 siblings. All survivor treatment exposure groups (chemotherapy alone, chemotherapy with cranial or craniospinal radiotherapy) had decreased adult height (height SDS < -2) compared with siblings ($P <0.001$). Among survivors, significant risk factors for short stature included diagnosis of ALL before puberty, higher-dose

	cranial radiotherapy (=20 Gy versus < 20 Gy), any radiotherapy to the spine, and female sex. Growth deficiency in children treated for ALL has been reported also from other geographic regions: Vilela and Viana (2007) found height deficit at the end of the therapeutic treatment in 129 children analyzed from a total of 351 cases diagnosed between 1987 and 1994 in Brazil.
Risk factors and risk groups	Especially pre-pubertal age group.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8. Close monitoring of growth in pediatric patients is recommended in SmPC Section 4.4 and PL Section 2. **Additional risk minimization measures:** None.

Table 13-5 Important potential risk Reproductive toxicity/pregnancy

Evidence for linking the risk to the medicine	This risk has been observed in preclinical and clinical studies. **Literature evidence:** Epidemiologic data regarding pregnancy outcomes are not available on untreated patients with CML. Most of the published data on the prevalence of various pregnancy outcomes are from patients treated with imatinib. Among men, an early report of Novartis data described 13 pregnancies in the partners of men who were taking imatinib at conception. The outcome was known for only 8 of these; 3 ended in abortion (two therapeutic and one spontaneous), one in utero death occurred at 13 weeks, and four normal pregnancies resulted in four normal infants. In contrast, a later report from M.D. Anderson noted seven normal pregnancies and one spontaneous abortion in the partners of eight men treated with imatinib for a median of 20 months. One infant was born with a malrotation of the gastrointestinal tract, which required surgical correction. Subsequently, 10 additional uneventful pregnancies were reported in the partners of 9 men on both standard and high doses of imatinib (Apperley 2009). Among women, Ault et al (2006) reported their experience on 10 women who conceived while receiving treatment for imatinib, all of whom discontinued therapy on recognition of pregnancy. Two had spontaneous abortions, one had an elective abortion. All the other pregnancies were uneventful. One infant was noted to have hypospadias. Subsequently, Pye et al (2008) reported pregnancy outcomes data on 125 (69%) of 180 women exposed to imatinib during pregnancy. Among women with known outcomes, 50% delivered normal infants and 28% underwent elective terminations (3 patients following the identification of abnormalities). Abnormalities were identified in 12 infants, 3 of whom had strikingly similar complex malformations (exomphalos and vertebral abnormalities (scoliosis/hemivertebrae) with or without abnormalities of the kidney (absent right kidney or right renal agenesis, duplex left kidney), hypoplastic lungs and shoulder anomaly). Eighteen pregnancies (14.4% of pregnancies with known outcomes) ended in spontaneous abortion (Pye et al 2008, Apperley 2009).

	In the general population, according to the CDC (2008), the overall prevalence of major defects was 3.0 per 100 in 2005 in the MACDP. This program monitors the prevalence of all major structural or genetic defects at the time of delivery among live births, stillbirths, and pregnancies electively terminated after prenatal diagnosis of defects at ≥20 weeks' gestation in the five central counties of metropolitan Atlanta. MACDP defines major structural or genetic birth defects as conditions that 1) result from a malformation, deformation, or disruption in one or more parts of the body, a chromosomal abnormality, or a known clinical syndrome; 2) are present at birth; and 3) have a serious, adverse effect on health, development, or functional ability. EUROCAT is a European network of population-based registries for the epidemiologic surveillance of congenital anomalies that was started in 1979 and has surveyed more than 1.7 million births surveyed per year in Europe. It includes data from 43 registries in 23 countries and covers 29% of the European birth population. EUROCAT reported that the prevalence of all anomalies was 2.56 (95% CI: 2.55-2.58) per 100 births (live births , fetal deaths/still births from 20 weeks gestation and termination of pregnancy for fetal anomaly following prenatal diagnosis) (EUROCAT 2014). In the general population, spontaneous abortion is the most common complication of early pregnancy, its frequency decreasing with increasing gestational age. Eight to 20 percent of clinically recognized pregnancies at less than 20 weeks of gestation undergo spontaneous abortion with 80% of these occurring in the first 12 weeks of gestation. The overall risk of spontaneous abortion after 15 weeks is low (about 0.6%) for chromosomally and structurally normal fetuses, but varies with the presence of associated risk factors. Loss of unrecognized or subclinical pregnancies occurs in 13 to 26% of all pregnancies. If pre-implantation losses are considered, approximately 50% of fertilized oocytes do not result in a live birth (Tulandi and Al-Fozan 2013).
Risk factors and risk groups	Female patients of reproductive age.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 SmPC Section 5.3 SmPC Section 4.6 and PL Section 2 recommend usage of highly effective contraception and also that nilotinib should not be used during pregnancy unless it is highly required. **Additional risk minimization measures:** None.

Table 13-6 Important potential risk Skin malignancy

Evidence for linking the risk to the medicine	This risk has been observed in preclinical and clinical studies. **Literature evidence:** Based on SEER data for the period 1973-2000, the incidence of melanoma of the skin in the US was not statistically significantly higher in patients with CML when compared with the general population (SIR: 1.03, p>0.05; IR: 28.7 cases per 100,000 patient-years) (Ishibe and Curtis 2006). In a population-based study by Rebora et al (2010) that included CML patients from the Swedish Cancer Registry diagnosed

	between 1970 and 1995, the SIR showed a higher risk of melanoma, although again it was not statistically significantly higher compared with the general population (SIR: 1.40, 95% CI: 0.29 4.09; IR: 33.0 cases per 100,000 patient-years). In the case of other skin malignancies, including SCC and BCC, the risk was higher in CML patients compared with the general population (SIR: 5.36, 95% CI: 3.18-8.47; IR: 197.9 cases per 100,000 patient-years) (Rebora et al 2010). At a US hospital, among 1,342 patients with CML treated between 1998 and 2010, 14 cases of NMSC (BCC or SCC) were observed after a median of 107 months of follow-up (Verma et al 2011).
Risk factors and risk groups	This risk has been observed in pre-clinical and clinical studies. Having a personal history of NMSC, including BCC or SCC, is an independent risk factor for the development of secondary cancers (Chen et al 2008, Wheless et al 2010). Evidence from the literature also suggests that NMSC at earlier age is associated with a higher risk of developing a secondary cancer. NMSC was associated with a statistically significantly increased risk in all age groups, but the relative risks were strongest in the younger age groups (Chen et al 2008).
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 5.3. **Additional risk minimization measures:** None.

Table 13-7 Missing information: Pediatric patients below 2 years of age

Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.2 **Additional risk minimization measures:** None.

13.2.3 Part VI – II C: Post-authorization development plan

13.2.3.1 II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Tasigna.

13.2.3.2 II.C.2. Other studies in post-authorization development plan

There are no studies required for Tasigna.

Annex 4 - Specific adverse drug reaction follow-up forms

Significant bleeding

Tasigna targeted follow-up checklist for significant bleeding (ver 2.0/October 2016)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Event Description:

Were any of the following diagnostic tests performed? **Check all that apply and please specify which test(s), dates and results**

- ☐ Blood tests
- ☐ Coagulation inhibitors level (antithrombin III, C protein, S protein), auto-antibodies, circulating anticoagulants
- ☐ Chest x-ray
- ☐ Doppler ultrasound
- ☐ Coagulation tests (PT/PTT, INR)
- ☐ Euglobulin lysis time
- ☐ CT scan
- ☐ ECG
- ☐ None of the above

Patient History:

Does the patient have a history of any of the following? **Check all that apply**

- ☐ Ulcer
- ☐ Surgery
- ☐ Hereditary and familial disorders (i.e. hemophilia and factor deficiencies) *(please specify)*
- ☐ Hemolytic disorders
- ☐ Diverticulosis
- ☐ Bleeding disorders/abnormal coagulation tests
- ☐ Cancer
- ☐ Trauma
- ☐ DIC
- ☐ Platelet disorders
- ☐ Varices
- ☐ Vitamin K deficiency
- ☐ Other relevant history *(please specify)*

Was the patient taking any of the following drugs at the time of the event or in the past 30 days?? **Check all that apply**

- ☐ Oral contraceptives/HRT
- ☐ Corticosteroids
- ☐ NSAIDs
- ☐ Anticoagulants including aspirin
- ☐ Antibiotics
- ☐ Chemotherapy
- ☐ Antihypertensive agents
- ☐ None of the above

Current Medication:

When was last dose taken prior to event: _____AM _____PM
amount of time between dose & food_____

When was the previous dose taken: _____AM _____PM
amount of time between dose & food_____

Time of last meal prior to event_____

Has patient taken grapefruit juice ☐ or supplements containing grapefruit extract ☐ while taking Tasigna?

Has Tasigna been interrupted since start of therapy prior to this event? ☐ No ☐ Yes
If yes, date:_____ Reason for change:_____
Date resumed:_____ Dose & frequency:_____

How long was patient on Tasigna prior to the adverse event (total time)? _____

Severe infections

Tasigna Targeted Follow-up Checklist for Severe Infections (ver 2.0/July 2016)

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Event Description:

Summary of clinical course *(please include corresponding dates)*:

- Diagnosis
- Treatment, including response to standard therapy
- Outcome

Were any of the following diagnostic tests performed? **Check all that apply and please specify which test(s), dates, results, and reference range and units if applicable**

☐ Full blood count
☐ Culture of blood, urine and other bodily fluids (e.g. cerebrospinal, peritoneal, pleural)
☐ Specialized serologic tests
☐ PCR for infectious agent
☐ Imaging studies (e.g. MRI, CAT or CT)
☐ None of the above

Relevant medical history (concurrent and pre-existing conditions)
(Please specify medical condition and date of onset)
Check all that apply and please describe:

☐ Recurrent infections or chronic infections
☐ Poor nutritional status (e.g. BMI < 21)
☐ Corticosteroid use
☐ Trauma with open wound or burns
☐ Peripheral vascular disease
☐ Other relevant history *(please specify)*
☐ Invasive devices (e.g. on dialysis, catheter or feeding tube)
☐ Traveling or contact with contagious agents
☐ Weakened immune system (e.g. HIV/AIDS)
☐ Chronic disease (e.g. diabetes)
☐ None of the above

Current Medication:

When was last dose taken prior to event: _____AM _____PM
amount of time between dose & food_____

When was the previous dose taken: _____AM _____PM
amount of time between dose & food_____

Time of last meal prior to event_____

Has patient taken grapefruit juice ☐ or supplements containing grapefruit extract ☐ while taking Tasigna?

Has Tasigna been interrupted since start of therapy prior to this event? ☐ No ☐ Yes
If yes, date:_____ Reason for change:_____
Date resumed:_____ Dose & frequency:_____

How long was patient on Tasigna prior to the adverse event (total time)?
_____

Reproductive toxicity/pregnancy

Tasigna Pregnancy Notification Form (1.1)

PATIENT WHO TOOK TASIGNA (nilotinib): FATHER ☐ MOTHER ☐

1. MATERNAL INFORMATION

Date of Birth Date of last menstrual period Expected Date of Delivery

Method of contraception:
_____

Contraception used as instructed?
Yes ☐ No☐ Uncertain ☐

2. MEDICAL HISTORY (include information on familial disorders, known risk factors or conditions that may affect the outcome of the pregnancy. If none, mark as N/A)

3. PREVIOUS OBSTETRIC HISTORY (provide details on all previous pregnancies, including termination or stillbirth)

	Gestation Week	Outcome including any abnormalities
1		
2		
3		
4		

5		

4. DRUG INFORMATION (list all therapies taken prior to and during pregnancy)

Name of drug	Daily Dose	Date Started	Date Stopped	Indication	Treatment Start (week of pregnancy)	Treatment Stop (week of pregnancy)

5. PRENATAL INFORMATION

Have any specific tests, e.g. amniocentesis, ultrasound, maternal serum AFP, been performed during the pregnancy so far? Yes☐ No☐ Not Known☐

If Yes, please specify test date and results:

Test _____ Date ☐☐/☐☐/☐☐☐☐

Result _____

6. PREGNANCY OUTCOME

(a) Abortion: Yes☐ No☐ (b) Delivery: Yes☐ No☐

If Yes,
Therapeutic☐ Planned☐ Spontaneous ☐

If Yes,
Normal☐ Caesarean☐ Forceps/Ventouse ☐

Please specify the reason and any abnormalities (if known):

_____
_____
_____

Maternal complications or problems related to birth:

_____
_____
_____

Date of Abortion: ☐☐/☐☐/☐☐☐☐ Delivery at week: ☐☐

7. MATERNAL PREGNANCY ASSOCIATED EVENTS

If the mother experiences an SAE during the pregnancy, please indicate here and complete an SAE form and submit immediately

8. CHILD OUTCOME

Normal☐ Abnormal☐ Stillbirth☐

If any abnormalities, please specify and provide dates

Sex:Male☐ Female☐ Apgar Scores:

Height ⌊_⌋ cm 1 min ⌊_⌋

Weight ⌊_⌋ kg 5 min ⌊_⌋

Head circumference ⌊_⌋ cm 10 mins ⌊_⌋

9. ASSESSMENT OF SERIOUSNESS (OF PREGNANCY OUTCOME)

Non serious ☐ Involved prolonged inpatient hospitalization ☐ Results in persistent or significant disability/incapacity ☐

Life-threatening ☐ Mother died ☐ Stillbirth/neonate died ☐

Date of death ⌊_⌋ Date of death ⌊_⌋

Other Seriousness criteria Congenital anomaly/birth defect ☐ Other Significant medical events ☐

10. ASSESSMENT OF CAUSALITY (OF PREGNANCY OUTCOME)

Please indicate the relationship between pregnancy outcome

Unrelated ☐ Possibly* ☐ Probably* ☐ Definitely* ☐

If any of the fields marked * have been checked, the outcome is considered to be RELATED to the study drug.

11. ADDITIONAL INFORMATION

12. INFORMATION SOURCE

HCP Details:

Name _____

Address _____

Date of report

HCP Signature _____

Annex 6 - Details of proposed additional risk minimization activities

Not applicable.