EU RISK MANAGEMENT PLAN
FOR
ICLUSIG (PONATINIB)

RMP version to be assessed as part of this application: 25.0

Data lock point for this RMP	26 FEB 2026	Version number	25.0
Date of final sign-off	17 MAR 2026		

Rationale for submitting an updated RMP:

Extension of the chronic myeloid leukaemia (CML) indication to paediatric patients 6 years of age or older with chronic phase-CML (CP-CML).

Summary of significant changes in this RMP:

Part	Major changes in v.25.0 compared to v.24.1
Part I	
Table 1	The section is updated to amend the proposed indication and dosage in the EEA, and the pharmaceutical form(s) and strengths
Part II	
Module SI	
Table 2	The section is updated to include epidemiology information on paediatric patients with CML
Module SIII	The section is updated to include the paediatric study INCB 84344-102 demographics, baseline characteristics and overall extent of exposure
Module SIV	
SIV.1	The section is updated to include the paediatric study INCB 84344-102
SIV.3	The section is updated to add data on paediatric patients
Module SV	The section is updated to add the post-authorization exposure and total number of countries where ponatinib is approved as per a DLP of 13DEC2025

Part	Major changes in v.25.0 compared to v.24.1
Module SVII	
SVII.2	The section is updated to mention that Growth retardation was added as a new important potential risk
SVII.3.1	The section is updated to include Growth retardation as a new important potential risk. INCB 84344-102 clinical trial data and updated post-marketing data as per a DLP of 13DEC2025 were added
Module SVIII	The section is updated to add Growth retardation as a new important potential risk
Part V	The section is updated to amend the vascular occlusive events routine risk minimization activities as per the proposed Product Information and add the routine risk minimization measures for the new important potential risk of Growth retardation
Part VI	This section is amended as per the proposed Product Information and to add Growth retardation as a new important potential risk

Other RMP versions under evaluation:

No other RMP versions are currently under evaluation.

QPPV name: Achint Kumar

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

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LIST OF ABBREVIATIONS

Abbreviation	Term
ABL	C-Abl Proto-Oncogene
ADR	Adverse Drug Reaction
AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
AOE	Arterial Occlusive Event
AP	Accelerated Phase
APAC	Asia-Pacific
AUC	Area Under the Curve
BCRP	Breast Cancer Resistance Protein
BCR-ABL	Breakpoint Cluster Region-Abelson
BP	Blast Phase
BRVO	Branch Retinal Vein Occlusion
CD20	Cluster of Differentiation 20
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Maximum Observed Plasma or Serum Concentrations
CML	Chronic Myeloid Leukemia
CMR	Complete Molecular Remission
CNS	Central Nervous System
CP	Chronic Phase
CR	Complete Remission
CRVO	Central Retinal Vein Occlusion
CSR	Clinical Study Report
CVA	Cerebrovascular accident
CVC	Central Venous Catheter
CYP	Cytochrome P450
DDI	Drug-Drug Interaction
DHPC	Direct Healthcare Professional Communication
DL	Dose Level
DLP	Data Lock Point

Abbreviation	Term
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EFS	Event-Free Survival
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EU	European Union
EUTOS	European Treatment and Outcome Study
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
FLT3	Fms-like tyrosine kinase-3
GVHD	Graft Versus Host Disease
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional
HPLC	High Performance Liquid Chromatography
hERG	Human Ether-a-go-go Related Gene
IARC	International Agency for Research on Cancer
IC_{50}	Half Maximal Inhibitory Concentration
KIT	Kinase Receptor
LBP	Lymphoid Blast Phase
LV	Left Ventricular
MAA	Marketing Authorization Application
MAH	Marketing Authorisation Holder
MDS	Myelodysplastic Syndrome
MDR1	Multidrug Resistance Protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MM	Multiple Myeloma
MRD	Minimal Residual Disease
MS	Myeloproliferative Syndrome
NCI	National Cancer Institute

Abbreviation	Term
ND	Newly Diagnosed
NET	Neutrophil extracellular traps
NOAEL	No-observed-adverse-effect level
nM	Nano molar
OAT	Organic Anion Transporter
OATP	Organic Anion Transporting Polypeptides
OCT	Organic Cation Transporters
OI	Opportunistic Infection
OS	Overall Survival
PAC	Post-Authorization Commitment
PACE	Ponatinib Ph+ ALL and CML Evaluation
PBRER	Periodic Benefit Risk Evaluation Report
PCR	Polymerase Chain Reaction
PDGFR	Platelet-Derived Growth Factor Receptor
P-gP	P-Glycoprotein
Ph	Philadelphia Chromosome
PhV	Pharmacovigilance
Ph+	Philadelphia Chromosome positive
PICC	Peripherally Inserted Central Catheter
PK	Pharmacokinetics
PL	Package Leaflet
PPD	Pospartum Day
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PVD	Peripheral vascular disease
QD	Once a day
RET	Rearrenged during transfection
RI	Resistant/Intolerant
RMP	Risk Management Plan
SAE	Serious Adverse Event
SCT	Stem Cell Transplantation
SD	Standard Deviation

Abbreviation	Term
SEER	Surveillance, Epidemiology & End Reports
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
T3	Thyroid hormone triiodothyronine
TEAE	Treatment Emergent Adverse Event
TKI	Tyrosine Kinase Inhibitor
TKD	Tyrosine Kinase Domain
TSH	Thyroid Stimulating Hormone
UK	United Kingdom
US	United States
VCAM	Vascular Cell Adhesion Molecule
VEGF	Vascular endothelial Growth Factor
VEGFR	Vascular endothelial Growth Factor Receptor
VOE	Vascular Occlusive Event
VTE	Venous Thrombotic / Embolic Event

PART I PRODUCT OVERVIEW

Table 1: Product Overview

Active substance(s) (INN or common name):	Ponatinib
Pharmacotherapeutic group(s) (ATC Code):	L01EA05
Name of Marketing Authorisation Holder or Applicant:	Incyte Biosciences Distribution B.V.
Medicinal products to which this RMP refers:	ICLUSIG®
Invented name(s) in the European Economic Area (EEA):	Iclusig®
Marketing authorisation procedure :	Centralized procedure
Brief description of the product:	Chemical class: Ponatinib is an orally-available BCR-ABL TKI.
	Summary of mode of action: Ponatinib is a kinase inhibitor. Ponatinib inhibited the in vitro tyrosine kinase activity of ABL and T315I mutant ABL with IC50 concentrations of 0.4 and 2.0 nM, respectively. Ponatinib inhibited the in vitro activity of additional kinases with IC50 concentrations between 0.1 and 20 nM, including members of the VEGFR, PDGFR, FGFR, EPH receptors and SRC families of kinases, and KIT, RET, TIE2, and FLT3.
	Important information about its composition: Ponatinib was specifically designed to inhibit native as well as mutated forms of BCR-ABL kinase including the T315I mutant. Through direct inhibition of native BCR-ABL1 and its variants, ponatinib inhibits aberrant downstream signaling by reducing phosphorylated CRKL, thereby promoting apoptosis and cell death in BCR-ABL1–positive cells. A critical feature of ponatinib's design is the incorporation of multiple contact points with the ABL1 kinase domain, which balances and distributes overall binding affinity.
Hyperlink to the Product Information:	See proposed Product Information.

Indication(s) in the EEA:	Current: Iclusig® is indicated in adult patients with: • CP, AP, or BP CML who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation. • Ph+ ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation. Iclusig is indicated in combination with reduced-intensity chemotherapy in adult patients with newly diagnosed Ph+ ALL.
	Proposed: Iclusig is indicated as monotherapy in paediatric patients 6 years of age or older with CP-CML who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.
Dosage in the EEA	Current: See SmPC for details: Patients with CML and Ph+ ALL previously treated with other TKIs or who have the T315I mutation: • The recommended starting dose is 45 mg of ponatinib QD. For the standard dose of 45 mg QD, a 45 mg film-coated tablet is available. Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity. • Patients should be monitored for response according to standard clinical guidelines. • Discontinuing ponatinib should be considered if a complete haematologic response has not occurred by 3 months (90 days). • The risk of arterial occlusive events is likely to be dose-related. Reducing the dose of Iclusig to 15 mg should be considered for CP-CML patients who have achieved molecular response (MR2 i.e. ≤1% BCR-ABL1^{IS}) taking the

	following factors into account in the individual patient assessment: cardiovascular risk, side effects of ponatinib therapy, time to response, and BCR-ABL transcript levels. If dose reduction is undertaken, close monitoring of response is recommended. In patients with loss of response the dose of Iclusig can be re-escalated to a previously tolerated dosage of 30 mg or 45 mg orally once daily. Iclusig should be continued until loss of response at the re-escalated dose or unacceptable toxicity. Patients with Newly-diagnosed Ph+ ALL in combination with chemotherapy: • The recommended starting dose is 30 mg of ponatinib once daily in combination with chemotherapy with a dose reduction to 15 mg once daily upon achievement of MRD-negative complete response (≤0.01% BCR-ABL1) at the end of induction. • Patients with loss of MRD negativity can re-escalate the dose of ponatinib to a previously tolerated dosage of up to 30 mg once daily. After completion of ponatinib in combination with chemotherapy, continue treatment with ponatinib as monotherapy until loss of response at the re-escalated dose or unacceptable toxicity. • CNS prophylaxis or treatment, steroid induction, anti-CD20 therapy in CD20+ patients or chemotherapy as applicable should follow the respective Summaries of Product Characteristics and standard clinical guidelines. • Discontinuing ponatinib should be considered if a complete molecular response has not occurred after the induction phase.
	Proposed: Current dosage in adults. Paediatric patients with CP-CML: • Ponatinib is administered orally once daily in the form of either Iclusig film-coated tablets or Iclusig hard capsules.

	The recommended starting dose is individualized for each paediatric patient on the basis of body weight. • There is no experience with treatment of paediatric patients below 6 years of age. • Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity. • Patients should be monitored for response according to standard clinical guidelines. • As in adults, the risk of arterial occlusive events is likely to be dose related. Reducing the dose of Iclusig should be considered for paediatric CP-CML patients who have achieved a molecular response taking the following factors into account in the individual patient assessment: cardiovascular risk, side effects of ponatinib therapy, time to response, and BCR-ABL transcript levels. If dose reduction is undertaken, close monitoring of response is recommended. In patients with loss of response the dose of Iclusig can be re escalated to a previously tolerated dosage. Iclusig should be continued until loss of response at the re escalated dose or unacceptable toxicity.
Pharmaceutical form(s) and strengths	Current: Ponatinib is available as 15mg, 30mg, or 45mg round, white, biconvex, round film-coated tablets.
	Proposed: Ponatinib is available as 5mg hard capsules or 15mg, 30mg, and 45mg film-coated tablets.
Is/will the product be subject to additional monitoring in the EU?	No

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Chronic myeloid leukemia and Philadelphia chromosome positive acute lymphoblastic leukaemia

Table 2: Chronic Myeloid Leukemia

<table>
<tr><th colspan="2">Chronic Myeloid Leukemia</th></tr>
<tr><td>Incidence</td><td>The incidence of CML ranges between 10 and 15 cases/10^6/year without any major geographic or ethnic differences. The median age at diagnosis ranges between 60 and 65 years in Europe, but is considerably lower in countries with a younger population. (ESMO Clinical Practice Guidelines 2017). According to the US National Cancer Institute's SEER statistic fact sheet on CML, 8,930 new patients were estimated to be diagnosed with CML in 2023 (National Cancer Institute (NCI). Cancer Stat Facts: Leukemia - Chronic Myeloid Leukemia (CML)).
Leukemia accounts for 29% of childhood cancers, with 76% being lymphoid leukemias (De Angelis et al 2014), whereas CML is relatively rare. It constitutes 2% of all leukemias in children younger than 15 years and 9% in adolescents aged 15 to 19 years, with an incidence of 1 and 2.2/10^6/year in these 2 age groups, respectively (Hijiya et al 2016).
CML represents about 15% of adult leukemias (Jabbour and Katarjian 2018); therefore, the incidence of CML can be estimated based on leukemia data. Table 3 highlights the approximate incidence rates of CML based on leukemia rates in select regions obtained from the IARC (Ferlay et al 2020).
Table 3: World age-Standardized Incidence Rate of Leukemia and CML per 100,000 people
<table>
<tr><th>Region</th><th>Leukemia incidence rate per 100,000 people</th><th>CML incidence rate per 100,000 people</th></tr>
<tr><td>World</td><td>5.4</td><td>0.8</td></tr>
<tr><td>Europe</td><td>7.6</td><td>1.1</td></tr>
<tr><td>Africa</td><td>3.2</td><td>0.5</td></tr>
<tr><td>Latin American, Caribbean</td><td>5.4</td><td>0.8</td></tr>
<tr><td>Northern America</td><td>10.9</td><td>1.6</td></tr>
<tr><td>Asia</td><td>4.7</td><td>0.7</td></tr>
<tr><td>Oceania</td><td>9.3</td><td>1.4</td></tr>
</table></td></tr>
<tr><td>Prevalence</td><td>The prevalence of CML is steadily rising due to the substantial prolongation of survival that has been achieved with targeted therapy (ESMO Clinical Practice Guidelines 2017). Although the prevalence of CML is not well known, it has been estimated to be 10-12/100,000 inhabitants in European CML registries (Hoglund et al 2015). Similar to incidence rates, the prevalence can</td></tr>
</table>

<table>
<tr><th colspan="2">Chronic Myeloid Leukemia</th></tr>
<tr><td></td><td>also be estimated through IARC data. Table 4 highlights the 5-year prevalence rates for CML based on Leukemia data.

Table 4: 5-year Prevalence of Leukemia and CML per 100,000 People
<table>
<tr><th>Region</th><th>Leukemia 5-year prevalence per 100,000 people</th><th>CML 5-year prevalence per 100,000 people</th></tr>
<tr><td>World</td><td>17.2</td><td>2.6</td></tr>
<tr><td>Europe</td><td>39.0</td><td>5.9</td></tr>
<tr><td>Africa</td><td>5.5</td><td>0.8</td></tr>
<tr><td>Latin American, Carabbean</td><td>16.6</td><td>2.5</td></tr>
<tr><td>Northern America</td><td>56.3</td><td>8.4</td></tr>
<tr><td>Asia</td><td>13.8</td><td>2.1</td></tr>
<tr><td>Oceania</td><td>40.4</td><td>6.1</td></tr>
</table>
Overall, there are over 200,000 CML patients in the world, over 43,000 in Europe, over 11,000 in Africa, over 31,000 in Northern America, over 96,000 in Asia, and over 2,000 in Oceania (Ferlay et al 2020).</td></tr>
<tr><td>Demographics of the population in the authorized indication</td><td>The median age of CML in Western countries is 57 years, while the median age in Asia and Africa is less than 50 years. In Western countries, 20% of all cases are above 70 years old while less than 5% of cases are in individuals under 18 years (Hochhaus et al 2020).

Incidence rates differ by sex and race in the US. US data from 2016-2020 indicate an incidence rate of 2.5 per 100,000 for males and 1.5 per 100,000 for females. In both males and females, non-Hispanics had the highest incidence rate (2.6 per 100,000 for males and 1.6 per 100,000 for females). In both sexes, non-Hispanic Asian/Pacific Islanders had the lowest incident rates (1.6 per 100,000 for males and 0.9 per 100,000 for females) (National Cancer Institute (NCI). Cancer Stat Facts: Leukemia - Chronic Myeloid Leukemia (CML)).

The EUTOS population-based registry was designed to study the incidence and clinical characteristic of CML patients in 20 European countries. All cases of newly diagnosed Philadelphia positive, BCR-ABL CML that occurred in a sample of 92.5 million adults living in 20 European countries, were registered over a median period of 39 months. 94.3% of the 2904 CML patients were diagnosed in CP. Median age was 56 years. 55.5% of patients had comorbidities, mainly cardiovascular (41.9%). High-risk patients were 24.7% by Sokal, 10.8% by EURO, and 11.8% by EUTOS risk scores. The raw incidence increased with age from 0.39/100 000/year in people 20-29 years old to 1.52 in those >70 years old, and showed a maximum of 1.39 in Italy and a minimum of 0.69 in Poland (all countries together: 0.99). The authors compared prognostic profiles of the identified CML patients with patients recruited for randomized trials, and did not notice a particularly positive selection of the population despite the difference in age: Sokal</td></tr>
</table>

Chronic Myeloid Leukemia	
	high-risk patients account for 24.7% of patients in the registry and for 17.9–27.7% in the randomized trials (Hoffman et al 2015).
Risk factors for the disease	One case control study examined the association between Helicobacter pylori infection and CML and suggested that gastric conditions including gastritis, peptic ulcers, and dyspepsia were associated with CML, with the Helicobacter pylori infection potentially being the common risk factor (Larfors et al 2020). Ionization radiation is also associated with CML (Chennamadhavuni et al 2024). Age and sex are other risks factor for CML, with older adults and male at a higher risk (Iezza et al 2023, Rohrbacher and Hasford 2009).
The main existing treatment options	Adult patients: The first line treatment for CML are TKIs. Four first-line TKIs have been approved by the FDA and EMA, including imatinib, dasatinib, nilotinib, and bosutinib. A fifth TKI, radotinib, is approved in South Korea. Second line treatment is possible following first line treatment failure or resistance; second line TKI treatment is patient dependent. Third line treatment includes ponatinib, which is more potent than first and second line TKIs. Ponatinib is approved for patients with first and second line TKI resistance and in patients with the BCR-ABL1 T315I mutation (Hochhaus et al 2020). In the absence of the T315I mutation, bosutinib and asciminib are alternatives to ponatinib for CML patients who are resistant or intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate. For CML patients who have the T315I mutation, the only alternative to ponatinib is asciminib. Generally, all TKIs are well tolerated, though, some may be associated with skin rash, fatigue, diarrhea, and cardiovascular adverse events (Narli et al 2023). Paediatric patients: Current guidelines recommend long-term targeted therapy with TKIs as first line treatment for pediatric CML (Smith et al 2021). The introduction of treatment with imatinib, a first-generation TKI reported very high response rates for the treatment of CML in children and adolescents (Suttorp et al 2011); however, the initial presence or the development of resistance to imatinib due to mutations in the kinase domain is a common cause of disease recurrence (Miller et al 2014). Reports show that 30% of patients with CP-CML discontinued imatinib mainly due to suboptimal response and development of resistance due to mutations in the kinase domain (Millot et al 2011). Second-generation BCR–ABL inhibitors have been developed and nonclinical studies of approved second-generation TKIs – dasatinib, nilotinib, and bosutinib – have demonstrated that these agents are more potent inhibitors of native BCR–ABL than imatinib and inhibit many, though not all, imatinib-resistant BCR-ABL mutants (O'Hare◦et al 2007, Cortes et al 2011). However, dasatinib, nilotinib, and bosutinib are ineffective against the T315I BCR-ABL mutant. There are limited approved therapeutic options for children with CML who are resistant or intolerant to second-generation TKI therapy or carry the T315I mutation.
Natural history of the indicated condition in the	Approximately half of CML patients are asymptomatic; CML is typically diagnosed during routine care. Over 90% of patients are diagnosed in the CP-CML. CML symptoms include fatigue, left upper quadrant pain, and malaise. Other symptoms

Chronic Myeloid Leukemia	
untreated population, including mortality and morbidity	can include bleeding, thrombosis, and gouty arthritis. AP-CML may include worsening anemia and CP-CML symptoms. In the BP-CML, patients have even worse symptoms, infections, fever, and bleeding (Jabbour and Katarjian 2018). Prognostic factors for CML include age, platelet count, blast cells proportion and spleen size. Furthermore, prior treatment failure is associated with subsequent treatment failure, leading to poorer prognosis (Iezza et al 2023). Based on US data from 2016-2020, the mortality rate is 0.3 per 100,000 men and women per year. The median age at death for CML was 77 years. Among all deaths, approximately 0.2% died under age 20; 2.2% between ages 20 to 34; 3.7% between ages 35 to 44; 6.2% between ages 45 to 54; 11.9% between ages 55 to 64; 18.9% between ages 65 to 74; 30.6% between ages 75 to 84; and 26.1% in patients 84+ years of age. For all races, mortality was twice as high for men as for women (0.4 compared to 0.2 per 100,000) (National Cancer Institute (NCI). Cancer Stat Facts: Leukemia - Chronic Myeloid Leukemia (CML)). Comorbid conditions are also associated with increased mortality in CML patients. Patients with higher scores on the Charlson Comorbidity Index were associated with lower overall survival (Iezza et al 2023). The introduction of TKIs has substantially reduced the mortality of CML. In the TKI therapy era the annual mortality rate on TKI therapy compared with an age-matched normal population was approximately 1.53 (Huang et al 2012).
Important co-morbidities	As the prevalence of CML increases with age, comorbidities associated with aging might be often present in patients when CML is diagnosed: cardiovascular disease, cancer, arthritis, cataracts, osteoporosis, type 2 diabetes, hypertension, and Alzheimer's disease (Valent 2011). Comorbidities were reported in the EUTOS population-based registry: In a sample of approximately 3,000 CML patients, 55.5% of patients had comorbidities, mainly cardiovascular (41.9%). Hypertension (25.7%), other cardiovascular disorders (17.2%), and diabetes mellitus (9.5%) were the most frequent comorbidities. Furthermore, 18% of all patients were current smokers, and 16% were former smokers (Hoffman et al 2015).

Table 5: Ph+ Acute Lymphoblastic Leukemia

Ph+ ALL	
Incidence	The estimated overall incidence of ALL and lymphoblastic lymphoma in Europe is 1.28 per 100 000 individuals annually, with significant age-related variations (0.53 at 45–54 years, ~1.0 at 55–74 years and 1.45 at 75–99 years (ESMO Clinical Practice Guidelines 2016). In the US, ALL accounts for 0.3% of all new cancer cases. The rate of new cases per year ranges from 1.5 to 1.9 per 100,000 persons over the last 20 years. In 2020, the age-adjusted rate of new cases was 1.8 per 100,000 persons (National Cancer Institute (NCI). Cancer Stat Facts: Leukemia – Acute Lymphocytic Leukemia (ALL)). ALL is the most common cancer diagnosed in children and represents 25% of cancer diagnoses among children younger than 15 years. ALL is the most common childhood leukemia, accounting for three-fourths of all childhood leukemias

Ph+ ALL	
	(Canadian Cancer Society-risks for childhood leukemia). In the US, ALL occurs at an annual rate of approximately 40 cases per 1 million people aged 0 to 14 years and approximately 21 cases per 1 million people aged 15 to 19 years. There are approximately 3,100 children and adolescents younger than 20 years diagnosed with ALL each year (National Cancer Institute (NCI). Childhood Acute Lymphoblastic Leukemia Treatment (PDQ®)–Health Professional Version). ALL occurs at any age, but its incidence increases at age 50 and older (Canadian Cancer Society-risks for acute leukemia). Rates of ALL vary globally. The highest rates of ALL are in developed countries, included Spain, US, Canada, and New Zealand. The lowest rates are found in developing countries. Childhood ALL is most common in Costa Rica, while the lowest rate of childhood ALL are found in the Middle East and India (Wartenberg et al 2008). Since 1975, there has been a gradual increase in the incidence of ALL. A sharp peak in incidence observed among children aged 1 to 4 years (81 cases per 1 million per year), with rates decreasing to 24 cases per 1 million by the age of 10 years. The incidence of ALL among children aged 1 to 4 years is approximately fourfold greater than that for infants and for children aged 10 years and older. The incidence of ALL appears to be highest in American Indian or Alaska Native children and adolescents (65.9 cases per 1 million). The incidence is substantially higher in white children than in black children, with a two-fold higher incidence of ALL from age 1 to 4 years in white children than in black children (National Cancer Institute (NCI). Childhood Acute Lymphoblastic Leukemia Treatment (PDQ®)–Health Professional Version). The Ph+, marked by the t(9;22)(q34;q11.2), is the most frequent chromosome abnormality in adult ALL. It is detected in 11% to 34% of patients with ALL, with increased prevalence in patients older than age 60 (Wetzlar 2008). Approximately 3% of children with ALL have Ph+ ALL, with approximately 90% having the “ALL-type” break points that produce p190 BCR-ABL1. Furthermore Ph+ ALL accounts for approximately 15%-25% of adult ALL cases, with rates starting to increase in adolescence (Hunger 2011).
Prevalence:	According to the US National Cancer Institute's SEER statistic fact sheet on ALL, in 2021, there were 115,294 individuals in the US with ALL (National Cancer Institute (NCI). Cancer Stat Facts: Leukemia – Acute Lymphocytic Leukemia (ALL)).
Demographics of the population in the authorized indication	Acute lymphoblastic leukemia is more common in countries with a high human development index. Among males, the highest rates are in Ecuador, Costa Rica and Columbia. In Females, the highest rates are in Ecuador, Cyprus, and Costa Rica. Males and females have similar incidence rates until age 65; after age 65 males have a notably higher rate. The incidence rates peaks in both males and females between ages 0-4 and around 75 years of age (Miranda-Filho et al 2018). ALL is more common among those of European descent than African descent (Hourigan and Goldstone 2011) Based on US data from 2017-2021, the median age at diagnosis for acute lymphocytic leukemia was 17 years of age. Among all patients, approximately 53.0% were diagnosed under age 20; 11.1% between ages 20 to 34; 6.6% between ages 35 to 44; 6.8% between ages 45 to 54; 8.4% between ages 55 to 64; 8.1%

Ph+ ALL	
	between ages 65 to 74; 4.5% between ages 75 to 84; and 1.5% of patients 84+ years of age. Males had a higher incident rate than women (2.1 and 1.6 per 100,000, respectively). Across genders, Hispanics had the highest incidence rates, following by non-Hispanic American Indian/Alaska Native. Non-Hispanic blacks had the lowest incidence rates of ALL in both sexes (National Cancer Institute (NCI). Cancer Stat Facts: Leukemia – Acute Lymphocytic Leukemia (ALL)). In Europe, one Italian study revealed a peak in the incidence of ALL in the age groups 1-5 and 5-10, with a progressive decrease from 10 to 30 years and an increase from 30 years onwards. Gender distribution highlighted an overall lower incidence of females: this phenomenon was remarkable between 14-50 years and disappeared in the 50-60 age-cohort (Foà 2011). Another study conducted a data analysis from the Croatian population diagnosed with ALL from 2005 to 2009 presented a bimodal pattern with 51% cases aged 0-19 and 21% cases in the 65+ age group (Novak et al 2012).
Risk factors for the disease	While the cause of ALL in adults is unknown, there are several risk factors associated with ALL. Maternal age and cigarette smoking may be associated with offspring with a higher risk of ALL. Additionally, first born babies and babies with a higher birth weight are associated with an increased risk of ALL (Wartenberg et al 2008, Hourigan and Goldstone 2011). Down syndrome and other genetic conditions (for example Shwachman syndrome, Bloom syndrome), as well as inherited genetic polymorphisms are potential risk factors for the development of ALL. Children with Down syndrome have an increased risk of developing ALL and AML with a cumulative risk of developing leukemia of approximately 2.1% by age 5 years and 2.7% by age 30 years. Approximately one-half to two-thirds of cases of acute leukemia in children with Down syndrome are ALL (National Cancer Institute (NCI). Childhood Acute Lymphoblastic Leukemia Treatment (PDQ®)–Health Professional Version). Exposure to chemicals, pollution, and diet may also increase the risk of ALL; however, studies may not be conclusive and do not focus solely on ALL (Wartenberg et al 2008).
The main existing treatment options	<u>Newly-diagnosed Ph+ALL patients:</u> The TKI imatinib is an integral part of front-line therapy for Ph+ ALL, with good remission rates irrespective of whether imatinib is given alone or combined with chemotherapy. Treatment outcome with imatinib-based regimens has improved compared with historic controls, but most patients who do not undergo allogeneic SCT eventually relapse. Acquired resistance on TKI treatment is associated with mutations in the BCR-ABL TKD in the majority of patients, and may be detected at low frequency prior to TKI treatment in a subset of patients. The second generation TKI, dasatinib, shows activity against most of the BCR-ABL TKD mutations involved in acquired imatinib resistance, but clinical benefit is generally short-lived. Accordingly, SCT in first CR is considered to be the best curative option. Molecular monitoring of MRD levels appears to have prognostic relevance and should be used to guide treatment. Mutation analysis during treatment relies increasingly on highly sensitive PCR techniques or denaturing HPLC and may assist in treatment decisions, eg, in case of molecular relapse. Ponatinib is a potent, third-generation inhibitor of BCR-ABL that is active against all single allele mutations of the ABL1 gene. Early efficacy of the combination of chemotherapy plus ponatinib has been reported in adults with Ph+ ALL. Trends toward durable responses and an early,

Ph+ ALL	
	positive trend in EFS further support the potential benefit of ponatinib compared to imatinib in ponatinib-3001 Study. Strategies to improve outcome after SCT include the pre-emptive use of imatinib, dasatinib or ponatinib which appears to reduce the relapse rate. Resistant/Intolerant (RI) Ph+ALL patients: There are no approved alternatives to ponatinib for Ph+ ALL patients who are resistant or intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate. However there are investigational chemotherapy free treatments which seem to provide very promising results: Off label therapeutic options under investigation: Blinatumomab plus ponatinib: Interim results of a Phase 2 study. A study for frontline treatment and for relapsed/refractory (R/R) and CML-Lymphoid Blast Phase (LBP) patients with Ph+ ALL (n=35). Analysis included 28 patients (median age: 59 years). Overall, 95% of patients responded; the CR/CRi rate was 100% in the newly diagnosed (ND) cohort and 88% in the R/R cohort. 86% of responding patients achieved CMR (87% in the ND cohort and 86% in the R/R cohort). Median time to CMR: 1 month. Estimated 1-year OS rate was 94% and EFS rate was 81% for the entire study cohort. In the ND cohort, the 1-year overall survival (OS) and event-free survival (EFS) rates were both 100%. In the RR cohort, 1-year OS and EFS rates were 88% and 55%, respectively. Treatment was well tolerated, and most side effects were grade 1-2 (Short N 2021). An effective chemotherapy-free regimen of ponatinib plus venetoclax for relapsed/refractory Philadelphia chromosome-positive acute lymphoblastic leukemia: Five of six patients (83%) who received the venetoclax 800 mg daily dose level achieved CR/CRi, none of whom have relapsed and all of whom remain in continuous remission without alloHSCT. These results compare favorably to the PACE trial of ponatinib monotherapy patients with relapsed/refractory Ph+ ALL in which responses were short-lived, with a median duration of response of only 3 months and a 1-year progression-free survival rate of <10%. Although the study involves a limited number of patients with a limited follow-up, the lack of any observed relapses in this cohort suggests durable clinical benefit of this novel, oral combination as compared to ponatinib monotherapy. These data are especially encouraging in the setting of the very heavily pretreated population enrolled in the present study (≥50% of patients having prior ponatinib exposure, prior blinatumomab exposure and/or prior alloHSCT) (Short NJ 2021).
Natural history of the indicated condition in the untreated population, including mortality and morbidity	Patients who have Ph+ ALL and are resistant or intolerant to prior dasatinib who have the T315I mutation have a poor long-term prognosis. Symptoms of ALL such as weakness or feeling tired, fever, easy bruising or bleeding, bleeding under the skin, shortness of breath, weight loss or loss of appetite, pain in the bones or stomach, pain or a feeling of fullness below the ribs, as well as painless lumps in the neck, underarm, stomach, or groin, may impair daily life activities and form an immediate health risk (US National Library of Medicine. MedlinePlus. Acute Lymphocytic Leukemia). Based on the US data from 2018-2022, the median age at death for ALL was 60 years of age. The age-adjusted death rate was 0.4 per 100,000 persons per year, both men and women. Approximately 13.2% of all ALL deaths are among patients under age 20; 12.3% between ages 20 to 34; 8.3% between ages 35 to 44; 9.0%

Ph+ ALL	
	between ages 45 to 54; 14.7% between ages 55 to 64; 18.3% between 65 and 74; 16.0% between ages 75 to 84; and 8.2% in patients 84+ years of age. In 2020, there were 1,390 ALL deaths, for a death rate of 0.4 per 100,000 persons (National Cancer Institute (NCI). Cancer Stat Facts: Leukemia – Acute Lymphocytic Leukemia (ALL)). In patients with ALL, the 5-year survival rate is 85% for patients aged 0-14, 61% for patients aged 15-19, 44% in patients aged 20-29, 40% in patients aged 30-39, 28% in patients aged 40-59, 19% in patients aged 60-69, and 6% in patients over 70. The overall survival of Ph+ ALL was 50%, compared to 73% for Ph- ALL (Sasaki et al 2021).
Important comorbidities	Based on the bimodal age distribution of ALL – younger than 19 and older than 65 years – comorbidities are different for ALL depending on the age of onset. Whereas in the younger age group genetic conditions most likely accompany ALL, in the elderly, aging-associated diseases such as cardiovascular disease, cancer, arthritis, cataracts, osteoporosis, type 2 diabetes, hypertension and Alzheimer's disease might be evident (Valent 2011).

PART II: MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

An overview of key safety findings from non-clinical studies and their relevance to human usage is presented in Table 6 below. Please note that only studies with relevant information are included.

Table 6: Non-clinical Safety Findings with Potential Relevance to Human Usage

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Pancreas Administration of 100 mg/kg in rats resulted in single-cell necrosis involving the exocrine pancreas and intestinal crypt epithelial cells in several of the early decedents. In a 28-day oral toxicity study of 1, 2.5 and 5 mg/kg/day in cynomolgus monkey, the 5 mg/kg/day dose level was not tolerated, with mortality/ moribundity occurring in 3 of 10 animals during the last 2 weeks of the study. A variety of of pancreatic alterations (acinar cell necrosis, fibrinous inflammation, fibrosis, and acinar atrophy) were noted in males at 5 mg/kg/day.	The pancreas was a target organ of toxicity in the non-clinical studies. The effects were confirmed by studies in humans, where pancreatitis was the dose limiting toxicity in the Phase 1 dose finding study. Adverse effects are adequately described in the current SmPC.
Thyroid In the cynomolgus monkey, follicular atrophy of the thyroid gland was noted in one of two female monkeys dosed with 15 mg/kg of ponatinib and in one of two males and two of two females dosed with 45 mg/kg of ponatinib. This change was graded as minimal to mild, with the higher intensity noted in females in the 45 mg/kg dose group. In a 28-day repeat dose toxicity study in rats, daily administration of 1.5 or 3 mg/kg of ponatinib resulted in slight decreases in the thyroid hormone T3 at the end of the dosing phase of the study. However, there were no histological correlates in the thyroid for these changes. In a 28-day oral toxicity study of 1, 2.5 and 5 mg/kg/day in cynomolgus monkey showed various histopathological changes in the thyroid gland of the 5 mg/kg group. A decrease in T3 was noted. Additional observations included non-dose-dependent thyroid gland follicular atrophy at 2.5 and 5 mg/kg (mostly accompanied by a	Decreased serum T3 values, which correlated to histological changes in the thyroid gland, in animals were not observed in clinical studies. In addition, TSH values were routinely measured in the phase 1 study and clinically relevant levels of increased TSH were not observed. From clinical trials, 25/763 (3.3%) patients experienced hypothyroidism, all these events were non-serious. From the phase 2 PACE study, 13 (2.9%) patients experienced hypothyroidism and "hypothyroidism" is included as a common ADR in the SmPC.

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
reduction in T3 levels and a tendency toward increased TSH levels).	
Musculoskeletal In a 28-day repeat dose toxicity study in rats histopathologic examination of tissues from animals in the 6 mg/kg/day dose group that were sacrificed on Days 9 or 10 revealed minimal to mild cartilaginous hyperplasia of the epiphyseal plate of the femur. At the end of the 28-day dosing period, hyperplasia of the epiphyseal plate of the femur was observed in three of seven females in the 3 mg/kg/day dose group. No ponatinib-related microscopic changes were observed in the 1.5 mg/kg/day dose group at the end of the dosing phase of the study. In the 6-month oral toxicology study in rats, ponatinib-related reduced chondrocytes in the physis with and without reduced trabecular bone of the femur were present at the 0.75 and 2 mg/kg/day dose levels. Histologic examination revealed decreased numbers of chondrocytes along the physis in the femur at the 0.75 and 2 mg/kg/day dose levels.	Hyper-/hypoplastic changes of the chondrocytes in the physis were noted in both rat studies. The effect is considered an age-dependent consequence of treating young rats that were immature at study initiation, and is an effect without relevance to adults.
Phototoxicity In pigmented rats, no dermal or ocular toxicity was observed at 2 mg/kg. The mean ponatinib plasma concentration at the time of light exposure was 73 ng/mL. This concentration is comparable to the mean C_{max} in humans (77 ng/mL) administered ponatinib at a daily oral dose of 45 mg. At 5 mg/kg, no signs of dermal toxicity were observed. A low level phototoxic reaction was observed in the form of lenticular epithelial hyperplasia. The mean ponatinib plasma concentration 8 hours postdose was 169 ng/mL. At 10 mg/kg, no signs of dermal toxicity were observed. A low level phototoxic reaction was observed in the form of corneal edema and inflammatory changes, and lenticular epithelial hyperplasia. The mean ponatinib plasma concentration 8 hours postdose was 380 ng/mL.	No evidence of cutaneous phototoxicity was found. Low level ocular phototoxicity was seen in the highest dose groups in the animal studies. Ocular phototoxicity was not reported in the clinical studies. Information on toxicologic findings are provided in the SmPC.

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Safety Pharmacology – *Cardiac* Ponatinib inhibited current in HEK-293 (human embryonic kidney) cells, which were stably transfected with hERG in a dose-dependent manner beginning with the 1.0 μM (1000 nM) concentration. The IC_{50} for ponatinib was 2.33 μM (2330 nM). This concentration is approximately 15 times higher than the mean C_{max} plasma concentration of ponatinib (145 nM; 77ng/ml) at the therapeutic dose of 45 mg and is not expected to be a factor at therapeutic plasma concentrations. Oral administration of ponatinib (0=vehicle, 2, 5, and 10 mg/kg) did not induce any significant effects on heart rate or systolic, mean, or diastolic arterial pressure in conscious telemetered Beagle dogs. Marginal (11% and 14%) increases in mean QTc were observed at 60 and 75 minutes post dose, respectively, in animals treated with the 10 mg/kg dose of ponatinib. The magnitude of these changes was not large enough to be considered biologically relevant. However, the mean values at these two time points are the result of only one animal having a 28 and 55% increase in QTc values at the 60 and 75 minutes post dose time points with the value returning to baseline 90 minutes postdose. There were no gross morphological changes in ECG tracings after the administration of ponatinib at 2, 5, and 10 mg/kg doses. Therefore, ponatinib at oral doses of 2, 5, and 10 mg/kg did not affect cardiac, circulatory functions or the electrocardiogram in conscious telemetered dogs with the possible exception of a transient increase in QTc value in one dog at the 10 mg/kg dose level. In the monkey acute toxicity study physical examinations performed on Day 13 post-dose revealed systolic heart murmurs (Grade II/VI) in one male in the 45 mg/kg dose group and one female in the 5 mg/kg dose group. Heart murmurs were also noted in some animals near the end of the 28-day repeat dose toxicity study on ponatinib in cynomolgus monkeys that were shown to be reversible during a 28-day non-treatment recovery period. It is unknown whether the murmurs were a primary effect of ponatinib or a secondary effect from stress or other physiologic factors.	Safety pharmacology studies in animals (mouse, rat, and monkey) did not show adverse effects with clinical relevance for humans with the possible exception of a transient increase in QTc value in one of four dogs at the 10 mg/kg dose level. However, the prolongation was not seen at the time of expected C_{max} and a causal attribution to ponatinib remains questionable. A review of central ECG monitoring and PK data collected in the phase 1 study by an external cardiology expert showed that ponatinib had no significant effect on QT prolongation. Additional information in relation to ECG changes/QT prolongation was collected during the phase 3 trial that was terminated and reviewed by the CHMP (in the framework of procedure EMEA/H/C/002695/II/0012). This additional data was considered consistent with previous evaluations that ponatinib does not prolong the QTcF interval. The significance of the systolic heart murmurs in the single dose and 28-day repeat dose study in monkeys remains unclear since heart murmurs were not reported in the clinical studies.

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Safety Pharmacology – *Vascular occlusion events* Treatment of primary murine endothelial cells in vitro with ponatinib at clinically effective concentrations: 1) measurably inhibited viability, 2) did not alter expression of coagulation factors thrombomodulin and tissue factor, or inflammatory cell adhesion molecules VCAM-1 and E-selectin, and 3) did not induce broad or robust secretion of inflammatory cytokines. Treatment of primary aortic smooth muscle cells in vitro with ponatinib at clinically effective concentrations did not enhance or inhibit their proliferation and/or survival. In vivo, twice daily dosing of ponatinib at 3 mg/kg or 15mg/kg for 14d enhanced carotid artery occlusion in a dose dependent manner in a photochemical-induced mouse model of thrombosis; however, these findings may have been due to non-specific toxicities as the mice were unexpectedly moribund at the usually well-tolerated doses. A subsequent study indicated that ponatinib does not potentiate photochemical-induced thrombosis in the carotid and femoral arteries of mice and rats, respectively. In a study evaluating the effects of ponatinib in a murine model of stenosis, ponatinib did not increase the incidence or severity of arterial neointimal formation in response to flow-mediated changes induced by partial carotid artery ligation in mice when compared to animals administered vehicle.	Following the VOEs observed in patients treated with ponatinib, these non clinical studies were performed to explore potential mechanisms of action causing these AEs. The results of these studies to date have not yielded a definitive conclusion regarding the pathway(s)/mechanism(s) of action causing vascular occlusion and therefore the clinical relevance of these exploratory non-clinical studies is still unknown.
Safety Pharmacology – *CNS* In murine studies, ponatinib was administered orally as a single dose at dose levels of 10, 30, and 100 mg/kg. Over 72 hours, ponatinib was shown to have no neuropharmacological effects or any effects on motor coordination at any dose level. A reversible decrease in spontaneous activity was observed 24 hours post-dose in the group of mice administered 100 mg/kg; the spontaneous activity was comparable to controls at later time points.	No safety issue was identified from the safety pharmacology studies regarding the CNS.

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Safety Pharmacology – Pulmonary system A study was performed to determine the potential effects of ponatinib on pulmonary function in conscious rats. No statistically significant or biologically relevant differences were observed between the drug treatment (3, 10, and 30 mg/kg) and vehicle control groups among the parameters (tidal volume, minute volume or respiratory rate) monitored.	No safety issue was identified from the safety pharmacology studies regarding the pulmonary system.
DDI	
<u>Cytochrome P450 System</u> Ponatinib was incubated with individual recombinant CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP 2D6, CYP3A4/5 and CYP2E1). Nearly 55% of ponatinib was metabolized by CYP3A4/5 at 60 min, which was identified as the main responsible cytochrome for ponatinib metabolism. A study to evaluate inhibition of specific CYP P 450 enzymes by ponatinib in human liver microsomes was conducted. Ponatinib was shown to be a reversible inhibitor of CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) with CYP2C19 most strongly inhibited. However, considering the C_{max} of ponatinib and observed inhibition constant K_i values, the coefficient (ratio of C_{max} and K_i) was uniformly <0.1 for all CYPs indicating that DDI due to reversible inhibition by ponatinib are highly unlikely at a human dose of 45 mg. Ponatinib is not a metabolism- or time-dependent inhibitor. A study in primary cultures of fresh human hepatocytes with ponatinib on the expression of cytochrome P450 (CYP) enzymes, showed that ponatinib, at pharmacologically relevant concentrations (up to 0.2 μM) did not induce CYP1A2, CYP2B6, CYP3A4 or MDR1 activity and/or mRNA levels. Results from a second study testing higher concentrations have again shown that CYP1A2, CYP2B6, and CYP3A4 are not induced by ponatinib at concentrations up to 5 μM, above which ponatinib was toxic to the hepatocytes.	Ponatinib is metabolized by the CYP P450 system, mainly by CYP3A4/5 and CYP2C8, CYP2C19, and CYP2D6 to a lesser extent. Therefore DDI are considered likely if ponatinib is given with strong CYP3A4/5 inhibitors or substrates. Non-clinical studies did not reveal an increased risk of other DDI. The potential risk of DDI via CYP3A4/5 is addressed in the SmPC.

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Transporter proteins The substrate and inhibitor potential of ponatinib towards the following transporters were assessed: P-gp, BCRP, OATP1B1 and OATP1B3, and OCT1. In addition, the inhibitor potential of ponatinib towards the following transporters was also assessed: bile salt export pump, OAT1 and OAT3, and OCT2. Ponatinib showed a concentration-dependent inhibition towards P-gp and BCRP, and the IC_{50} value was 0.491 μM (for P-gp) and less than 0.0165 μM (for BCRP). Ponatinib showed a concentration-dependent inhibition towards BSEP. Ponatinib was shown not to be a substrate of OATP1B1, OATP1B3, or OCT1, and also it was not an inhibitor of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, or OAT3.	In vitro, ponatinib is an inhibitor of P-gp and BCRP. Therefore, ponatinib may have the potential to increase plasma concentrations of coadministered substrates of P-gp or BCRP and is addressed in the current SmPC. Ponatinib is not expected to influence products that are substrates to other transporter proteins.
Influence of gastric pH Ponatinib displays pH-dependent aqueous solubility in vitro; as pH increases, ponatinib solubility decreases. The solubility of ponatinib HCl has been determined over the pH range between 1.2 and 7.5. Ponatinib HCl is highly soluble in aqueous solution at pH values less than 1.7 (equal to or greater than 7.79 mg/mL), slightly soluble at pH values between 1.7 and 2.7 (7.79 mg/mL to 0.00344 mg/mL) and insoluble above pH 3.7. These in vitro data suggest that concomitant administration of agents that alter gastric pH, including H2 antagonists and proton pump inhibitors, could affect ponatinib absorption. Gastric proton pump inhibitors have been shown to significantly reduce the absorption of other drugs with pH-dependent absorption.	A clinical study to evaluate the effect of multiple doses of lansoprazole (60 mg QD for 2 days), a potent suppressor of gastric acid secretion, on the single 45 mg dose of ponatinib in healthy subjects has been conducted. Overall, the relatively minor reductions in plasma ponatinib C_{max} (25%) without corresponding decreases in overall AUC that were observed are not believed to be important for clinical safety or efficacy. Ponatinib may be administered concurrently with drugs that raise gastric pH without the need for adjustment of ponatinib dose or separation of administration. This information is reflected in the current SmPC.
Displacement of human plasma-bound pontatinib by highly protein bound concomitant medications In vitro, ponatinib was not displaced from its plasma protein binding sites by other highly protein bound medications (ibuprofen, nifedipine, propranolol, salicylic acid, or warfarin).	Although this study was not done to address a particular safety concern, it does provide additional information that the distribution properties of ponatinib can be expected to be unaffected with concomitant use of protein-bound medications.

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
Extent of plasma protein binding and free ponatinib levels using plasma from hepatically impaired subjects Objective of study (ARP490) was to compare the *in vitro* plasma protein binding of ponatinib at 145 nM (geometric mean steady state C_{max} at the clinical therapeutic dose of 45 mg ponatinib QD) in plasma samples from subjects with normal hepatic function and with varying degrees of hepatic impairment (i.e., mild, moderate, and severe). Overall, there was no trend of increased ponatinib exposure in subjects with hepatic impairment.	*In vitro* data showed no difference in plasma protein binding in plasma samples of healthy subjects and hepatically impaired (mild, moderate and severe) subjects.
Fertility and reproduction and developmental toxicology	
A pilot dose range finding study and a definitive developmental toxicity study were performed in pregnant female rats to determine the effects of ponatinib on pregnancy and embryo-fetal development. Ponatinib was shown to be embryotoxic and fetotoxic when administered to pregnant rats at oral dose levels of 3 mg/kg/day (equivalent to the human AUC of 1296 ng.h/mL at the recommended starting dose of 45 mg/day). Fetal malformations were observed at oral doses of 1 (approximately 0.24 times the human AUC at 45 mg/day) and 3 mg/kg/day. <u>Male and female fertility</u> A pivotal fertility study was performed in male and female rats at 0.25, 0.75, and 1.5 mg/kg/day. The no-observed-adverse-effect level (NOAEL) for paternal toxicity was 0.25 mg/kg/day based on reduced body weight and reduced body weight gain at dose levels ≥0.75 mg/kg/day. Increased pre- and postimplantation embryo-fetal lethality was observed in the 1.50 mg/kg/day dose females. The NOAEL for reproductive performance and fertility was 1.50 mg/kg/day in males (AUC was 0.7x human AUC at the recommended starting dose of 45 mg/day) and 0.75 mg/kg/day in females (AUC was 0.1x human AUC at 45 mg/day). <u>Reproductive organs</u> Although there was no effect on male fertility	In nonclinical studies, embryo-fetal toxicities were observed. There are no adequate and well controlled studies of ponatinib in pregnant women. Women of childbearing potential should avoid becoming pregnant while taking ponatinib. The human relevance of the effects on female fertility parameters in rats is not known; clinical precautionary measures including effective female contraception are described in the SmPC. In the absence of effect on male fertility parameters in the rat fertility study, the testicular degeneration noted in the general toxicity study in monkeys is not considered to be of clinical relevance. It is of note that the testicular degeneration was only observed in the monkeys, and not in rats. It may be a secondary effect related to stress/cachexia in these animals. The results of the fertility studies are described in the updated SmPC.

Key Safety Findings (from non-clinical studies)	Relevance to Human Usage
parameters in the dedicated rat fertility study, a possible ponatinib-related effect in two male monkeys dosed at 5 mg/kg was noted mild degeneration of germ cell epithelium in the testes. Decreased numbers of spermatids were noted in seminiferous tubules in association with numerous spermatid giant cells.	
Juvenile toxicity	
Juvenile rats appear to be more sensitive to ponatinib toxicity than adults due to high plasma drug concentrations, but ponatinib did not adversely affect important developmental parameters in the juvenile toxicity study.	A pediatric investigation plan has been developed, and this juvenile rats study provides information on the possible need to reduce the starting dose for pediatric patients compared with adult patients.

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

Resistant/Intolerant (RI) CML and Ph+ALL adult patients:

Studies included in each analysis population are summarized below.

Resistant/Intolerant (RI) Ph+ ALL analysis adult population included the Ph+ ALL adult patients in Study AP24534-10-201 (phase 2, PACE) who received at least 1 dose of ponatinib monotherapy (n=32).

RI CML analysis adult population included the CML adult patients (including AP-CML, BP-CML, and CP-CML adult patients) in Study AP24534-10-201 and Study AP 24534-14-203 (phase 2, OPTIC) who received at least 1 dose of ponatinib monotherapy (n=699; 417 patients from Study AP24534-10-201 and 282 from Study AP 24534-14-203).

Overall analysis population included all enrolled adult patients who received at least 1 dose of ponatinib as monotherapy in the 2 studies: AP24534-10-201 and AP 24534-14-203.

Table 7: Demographics: Ponatinib Safety Population (RI CML and Ph+ALL adult patients) by Disease Group (N=731)

	RI Ph+ALL N=32	**RI-CML N=699**	**Overall N=731**
Age (years)[a]			
Mean (SD)	53.0 (19.15)	52.9 (15.14)	52.9 (15.32)
Median	61.5	54.0	54.0
Min-max	20-80	18-94	18-94
Age category: n (%)			
18 -< 45 years	10 (31.3)	215 (30.8)	225 (30.8)
45 - < 65 years	9 (28.1)	306 (43.8)	315 (43.1)
65 - < 75 years	11 (34.4)	137 (19.6)	148 (20.2)
≥ 75 years	2 (6.3)	41 (5.9)	43 (5.9)
Gender, n (%)			
Male	20 (62.5)	359 (51.4)	379 (51.8)
Female	12 (37.5)	340 (48.6)	352 (48.2)
Ethnicity, n (%)			
Hispanic/Latino	5 (15.6)	105 (15.0)	110 (15.0)
Not Hispanic/Latino	27 (84.4)	589 (84.3)	616 (84.3)
Missing	0	5 (0.7)	5 (0.7)
Race, n (%)			
White	31 (96.9)	543 (77.7)	574 (78.5)

	RI Ph+ALL N=32	RI-CML N=699	Overall N=731
Asian	1 (3.1)	101 (14.4)	102 (14.0)
Black or African American	0	31 (4.4)	31 (4.2)
American Indian or Alaska Native	0	2 (0.3)	2 (0.3)
Other	0	6 (0.9)	6 (0.8)
Unknown, Not Reported or Missing	0	16 (2.3)	16 (2.2)
Geographic region, n (%)			
North America (US + Canada)	18 (56.3)	214 (30.6)	232 (31.7)
South America	0	63 (9.0)	63 (8.6)
Europe	12 (37.5)	328 (46.9)	340 (46.5)
Asia + Oceania	2 (6.3)	94 (13.4)	96 (13.1)

[a] If age is not collected directly on eCRF, then age is calculated as the difference between date of birth and date of informed consent.

Data cut off dates: Study AP24534-10-201 (phase 2, PACE 06FEB2017) and Study AP24534-14-203 (phase 2, OPTIC, 15MAY2024)

Table 8: Baseline disease Characteristics: Ponatinib Safety Population (RI CML and Ph+ALL adult patients) by Disease Group (N=731)

	RI Ph+ALL N=32	RI-CML N=699	Overall N=731
ECOG Score			
0	11 (34.4)	475 (68.0)	486 (66.5)
1	17 (53.1)	191 (27.3)	208 (28.5)
2	4 (12.5)	32 (4.6)	36 (4.9)
≥ 3	0	1 (0.1)	1 (0.1)
History of Hypertension			
Yes	9 (28.1)	229 (32.8)	238 (32.6)
No	23 (71.9)	470 (67.2)	493 (67.4)
History of Diabetes			
Yes	5 (15.6)	67 (9.6)	72 (9.8)
No	27 (84.4)	632 (90.4)	659 (90.2)

	RI Ph+ALL N=32	RI-CML N=699	Overall N=731
History of Dyslipidemia			
Yes	4 (12.5)	147 (21.0)	151 (20.7)
No	28 (87.5)	552 (79.0)	580 (79.3)
History of Obesity			
Yes	7 (21.9)	171 (24.5)	178 (24.4)
No	25 (78.1)	528 (75.5)	553 (75.6)
Number of Cardiovascular Comorbidities			
≥ 1	18 (56.3)	359 (51.4)	377 (51.6)
≥ 2	6 (18.8)	180 (25.8)	186 (25.4)
≥ 3	1 (3.1)	59 (8.4)	60 (8.2)
4	0	16 (2.3)	16 (2.2)

Note: Baseline is defined as the last observation before first dose of study drug.
Note: Cardiovascular comorbidities included medical history of Diabetes Mellitus, Obesity, Hypertension, and Dyslipidaemia.
Data cut off dates: Study AP24534-10-201 (phase 2, PACE 06FEB2017) and Study AP24534-14-203 (phase 2, OPTIC, 15MAY2024)

Table 9: Overall Extent of Exposure: Ponatinib Safety Population (RI CML and Ph+ALL adult patients) by Disease Group (N=731)

	RI Ph+ALL N=32	RI-CML N=699	Overall N=731
Total Cumulative Dose (mg)			
Mean (SD)	6044.1 (9462.32)	22017.2 (20823.90)	21317.9 (20715.28)
Median	3577.5	14730.0	13290.0
Min-Max	135-52980	45-107850	45-107850
Dose Intensity (mg/day)[a]			
Mean (SD)	42.38 (7.284)	26.30 (11.860)	27.00 (12.148)
Median	45.00	26.38	27.43
Min-Max	17.7-51.6	3.4-47.0	3.4-51.6
Relative Dose Intensity (%)[b]			
Mean (SD)	94.18 (16.188)	69.63 (25.893)	70.70 (26.028)
Median	100.00	69.82	71.33
Min-Max	39.3-114.6	7.6-104.5	7.6-114.6

	RI Ph+ALL N=32	RI-CML N=699	Overall N=731
Duration of Exposure (days)[c]			
Mean (SD)	153.4 (227.04)	938.0 (811.00)	903.6 (810.48)
Median	81.0	679.0	610.0
Min-Max	3-1195	1-3203	1-3203
Patients treated with Iclusig for n (%)			
<1 month	3 (9.4)	26 (3.7)	29 (4.0)
1 to <3 months	14 (43.8)	53 (7.6)	67 (9.2)
3 to <6 months	8 (25.0)	71 (10.2)	79 (10.8)
6 to <12 months	3 (9.4)	100 (14.3)	103 (14.1)
12 to <24 months	3 (9.4)	94 (13.4)	97 (13.3)
≥24 months	1 (3.1)	355 (50.8)	356 (48.7)
Any Dose adjustement, n (%)			
Dose Reduction	4 (12.5)	469 (67.1)	473 (64.7)
Planned Protocol[d]	0	63 (9.0)	63 (8.6)
Dose Increased[e]	1 (3.1)	149 (21.3)	150 (20.5)
Dose Interrupted	9 (28.1)	521 (74.5)	530 (72.5)

[a] Dose Intensity = Total cumulative dose (mg) / Duration of Exposure (days).
[b] Relative Dose Intensity = [Total cumulative dose (mg) / expected total dose (mg)] x 100%. For Study AP24534-10-201, expected total dose is calculated using starting dose* duration of exposure. For Study AP24534-14-203, expected dose is calculated accounting for planned dose modification.
[c] Duration of Exposure = Last dose of study drug – first dose of study drug + 1.
[d] Dose was reduced upon achievement of response per protocol.
[e] Dose increases were allowed for 2 reasons: (1) Patients who had planned dose reduction per protocol, but with loss of response were allowed to dose increase or (2) Patients who recovered from related toxicities were allowed to dose increase to a dose no greater than baseline.
Data cut off dates: Study AP24534-10-201 (phase 2, PACE 06FEB2017) and Study AP24534-14-203 (phase 2, OPTIC, 15MAY2024)

As of 15MAY2024, in Study AP24534-14-203 (phase 2, OPTIC), 61 out of the 283 enrolled patients (21.6%) remained on study treatment, including 27 (28.7 %), 18 (18.9 %) and 16 (17.0 %) patients in cohort A (45 mg), cohort B (30 mg) and cohort C (15 mg) respectively.

Table 10: Duration of exposure phase 2 study (OPTIC) for different study reports

Study report (DLP)	Persons still on treatment	Duration of exposure (Mean [SD] – [Days])
Original study report (31MAY2020)	134	584.3 (392.31)
OPTIC 5 yr report (15MAY2024)	61	1071.7 (901.98)

Newly-diagnosed Ph+ALL adult patients:

The pivotal study (phase 3, Ponatinib-3001 [PhALLCON]) and the 2 supportive studies (phase 2, AP24534-11-001 [MDACC 2011-0030] and phase 2, INCB 84344-201 [GIMEMA LAL1811]) assess the efficacy and safety of ponatinib as 1L treatment in adult patients with Ph+ ALL except for adult patients in study AP24534-11-001 who had been previously treated for Ph+ ALL or CML (in accelerated phase or blast phase). A total of 294 adult patients have received ponatinib through these studies.

Table 11: Demographics and Baseline Characteristics: Ponatinib Safety Population (Newly-diagnosed Ph+ALL adult patients) by Study

	Ponatinib-3001* Ponatinib Arm (Cohort A) N=164[a]	**AP24534-11-001** Overall N= 87**	**INCB 84344-201*** Overall N= 44**
Age (years)			
Mean (SD)	51.2 (16.09)	48.0 (15.0)	65.0 (11.70)
Median	54.0	46.0	66.5
Min, max	19, 82	21,80	26, 85
Age category, n (%)			
18-<45	58 (35.4)	-	-
<50 years	-	50 (57.5)	5 (11.4)
≥45 to <60 years	45 (27.4)	-	-
≥50 to <60 years	-	17 (19.5)	-
≥60 years	61 (37.2)	20 (23.0)	-
≥50 to <65 years	-	-	13 (29.5)
≥65 to <75 years	-	-	18 (40.9)
≥75 years	-	-	8 (18.2)
Gender, n (%)			
Male	74 (45.1)	44 (50.6)	22 (50.0)
Female	90 (54.9)	43 (49.4)	22 (50.0)
Race, n (%)			
American Indian/ Alaska Native	2 (1.2)	-	NAV in DB
Asian	20 (12.2)	5 (5.7)	NAV in DB
Black/African American	9 (5.5)	6 (6.9)	NAV in DB
White	104 (63.4)	64 (73.6)	NAV in DB
Multiple	1 (0.6)	-	NAV in DB

	Ponatinib-3001* **Ponatinib Arm (Cohort A)** **N=164[a]**	**AP24534-11-001**** **Overall** **N= 87**	**INCB 84344-201***** **Overall** **N= 44**
Not reported	28 (17.1)	-	NAV in DB
Unknown	-	12 (13.8)	NAV in DB
Ethnicity, n (%)			
Hispanic/Latino	39 (23.8)	20 (23.0)	NAV in DB
Not Hispanic/Latino	105 (64.0)	56 (64.4)	NAV in DB
Missing/Not reported	15 (9.1)	11 (12.6)	NAV in DB
Unknown	5 (3.0)	-	NAV in DB
Geographic region, n (%)			
North America (US + Canada)	50 (30.5)	87 (100)	-
South America	21 (12.8)	-	-
Europe	71 (43.3)	-	44 (100.0)b
APAC	22 (13.4)	-	-
ECOG (WHO) performance status, n (%)			
0	72 (43.9)	22 (25.3)	23 (52.3)
1	85 (51.8)	54 (62.1)	17 (38.6)
2	7 (4.3)	11 (12.6)	3 (6.8)
Missing	-	-	1 (2.3)
Time since diagnosis of ALL (days)			
n	163	-	44
Mean (SD)	15.1 (9.94)	-	15.4 (9.72)
Median	12.0	-	13.5
Min, max	2, 63	-	5,66

* Source: Ponatinib-3001 CSR 11JUL2023 (cut off date 12AUG2022)
** Source: AP24534-11-001 CSR 15JUN2021 (cut off date 14DEC2020)
*** Source: INCB 84344-201 CSR addendum 27MAY2022 (cutoff date 30SEP2021)
[a] 164 patients were randomized to receive ponatinib. One patient died before receiving their first dose of study drug.
[b] Including Australia
SD: standard deviation; NAV: not available; DB: database.

Table 12: Overall Extent of Exposure: Ponatinib Safety Population (Newly-diagnosed Ph+ALL adult patients) by Study

	Ponatinib-3001* **Ponatinib Arm (Cohort A)** **N=163[a]**	**AP24534-11-001**** **Overall** **N= 87**	**INCB 84344-201***** **Overall** **N= 44**
Total cumulative Dose (mg)			
Mean (SD)	6176.3 (4726.82)	12584.0 (12749.58)	21039 (19205.9)
Median	4560.0	8520.0	14100
Range (Min-Max)	120, 32250	270, 52755	90, 73035
Dose Intensity (mg/day)[b]			
Mean (SD)	21.10 (6.914)	22.1 (8.99)	31.26 (10.402)
Median	19.28	18.4	30.47
Range (Min-Max)	5.5, 30.0	8, 45	13.6, 45.0
Relative Dose Intensity (%)[c]			
Mean (SD)	99.72 (1.513)	-	-
Median	100.00	-	-
Range (Min-Max)	81.9, 100.3	-	-
Duration of Exposure[d]			
Mean (SD)	11.88 (9.942) months	671.4 (701.63) days	753.1 (685.2) days
Median	7.25 months	398.0 days	415.0 days
Range (Min-Max)	0.1, 39.1 months	7, 2935 days	2, 2324 days
Dose modifications n (% of patients with at least one…)			
Interruption	129 (79.1)	-	25 (56.8)
Reduction Planned per protocol	108 (66.3) 47 (28.8)	- -	34 (77.3) -
Increased[e]	42 (25.8)	-	-
Interruption and reduction	-	-	24 (54.5)

* Source: Ponatinib-3001 CSR 11JUL2023 (cut off date 12AUG 2022)
** Source: AP24534-11-001 CSR 15JUN2021 (Cut off date 14DEC2020)
*** Source: INCB 84344-201 CSR addendum 27MAY2022 (cutoff date 30SEP2021)
Note: The enrolled population is defined as all patients who receive at least 1 dose of any study drug.
[a] 164 patients were randomized to receive ponatinib. One patient died before receiving their first dose of study drug.
b Dose Intensity = Total cumulative dose (mg) / Duration of Exposure (days).
c Relative dose intensity=total cumulative dose (mg) / expected total dose (mg) × 100%.
d Duration of Exposure = Last dose of study drug – first dose of study drug + 1.

e Dose increases were allowed for 2 reasons: (1) patients who had a planned dose reduction in ponatinib arm but had a loss of MRD negativity and were allowed to dose increase (ponatinib only). (2) patients who recovered from related toxicities were allowed to dose increase to a dose to no greater than baseline (ponatinib and imatinib).
Max: maximum; Min: minimum;
SD: standard deviation.

Paediatric patients:

The phase 1/2 study INCB 84344-102 assesses the efficacy and safety of ponatinib monotherapy for the treatment of recurrent or refractory leukemias or solid tumors in paediatric patients. A total of 61 paediatric patients have received ponatinib monotherapy through this study including 11 CP-CML patients.

Table 13: Demographics and Baseline Characteristics: Ponatinib Safety Population (paediatric patients; N=61)

Variable, n (%)	Phase 1					Phase 2[a]				Total (N = 61)
	Cohort 1 (≥ 12 to < 18 years)			Cohort 2 (≥ 6 to < 12 years)	Cohort 3 (≥ 1 to < 6 years)	Cohort 1 (≥ 12 to < 18 years)		Cohort 2 (≥ 6 to < 12 years)		
	DL 1[b] (N = 3)	DL 2[c] (N = 6)	DL 3[d] (N = 6)	DL 1[e] (N = 8[f])	DL 1[g] (N = 9)	CP-CML (N = 8)	Other Tumors (N = 14)	CP-CML (N = 2)	Other Tumors (N = 5)	
Tumor type										
Hematologic	0 (0.0)	1 (16.7)	0 (0.0)	2 (25.0)	1 (11.1)	8 (100.0)	2 (14.3)	2 (100.0)	2 (40.0)	18 (29.5)
Solid tumor	3 (100.0)	5 (83.3)	6 (100.0)	6 (75.0)	8 (88.9)	0 (0.0)	12 (85.7)	0 (0.0)	3 (60.0)	43 (70.5)
Age (years)										
n	3	6	6	8	9	8	14	2	5	61
Mean (SD)	15.0 (2.65)	14.3 (1.37)	15.5 (1.64)	8.6 (1.69)	3.4 (1.51)	14.6 (1.85)	14.5 (1.87)	11.0 (0.00)	8.2 (2.05)	11.6 (4.57)
Median (Min, Max)	16.0 (12, 17)	14.0 (13, 16)	16.0 (13, 17)	8.5 (6, 11)	4.0 (1, 5)	14.0 (12, 17)	14.5 (12, 17)	11.0 (11, 11)	9.0 (6, 10)	13.0 (1, 17)
Sex - n (%)										
Male	3 (100.0)	5 (83.3)	5 (83.3)	2 (25.0)	5 (55.6)	5 (62.5)	3 (21.4)	0 (0.0)	2 (40.0)	30 (49.2)
Female	0 (0.0)	1 (16.7)	1 (16.7)	6 (75.0)	4 (44.4)	3 (37.5)	11 (78.6)	2 (100.0)	3 (60.0)	31 (50.8)
Race - n (%)										
White/Caucasian	2 (66.7)	6 (100.0)	6 (100.0)	6 (75.0)	9 (100.0)	7 (87.5)	13 (92.9)	2 (100.0)	4 (80.0)	55 (90.2)
Black/African American	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Not Reported	1 (33.3)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (12.5)	1 (7.1)	0 (0.0)	1 (20.0)	5 (8.2)
Ethnicity - n (%)										
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (11.1)	0 (0.0)	1 (7.1)	0 (0.0)	3 (60.0)	6 (9.8)
Not Hispanic or Latino	2 (66.7)	4 (66.7)	6 (100.0)	6 (75.0)	8 (88.9)	7 (87.5)	13 (92.9)	2 (100.0)	1 (20.0)	49 (80.3)
Not Reported	1 (33.3)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	1 (20.0)	5 (8.2)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)

Table 13: Demographics and Baseline Characteristics: Ponatinib Safety Population (paediatric patients; N=61) (Continued)

Variable, n (%)	Phase 1					Phase 2[a]				Total (N = 61)
	Cohort 1 (≥ 12 to < 18 years)			Cohort 2 (≥ 6 to < 12 years)	Cohort 3 (≥ 1 to < 6 years)	Cohort 1 (≥ 12 to < 18 years)		Cohort 2 (≥ 6 to < 12 years)		
	DL 1[b] (N = 3)	DL 2[c] (N = 6)	DL 3[d] (N = 6)	DL 1[e] (N = 8[f])	DL 1[g] (N = 9)	CP-CML (N = 8)	Other Tumors (N = 14)	CP-CML (N = 2)	Other Tumors (N = 5)	
Body weight (kg) at baseline										
n	3	6	6	8	9	8	14	2	5	61
Mean (SD)	62.37 (17.823)	54.12 (6.472)	53.58 (17.322)	28.51 (7.725)	15.97 (3.772)	57.05 (13.530)	51.46 (14.104)	36.00 (15.556)	32.08 (9.328)	42.86 (18.887)
Median (Min, Max)	72.00 (41.8, 73.3)	52.90 (48.0, 64.4)	53.50 (27.0, 80.0)	28.70 (17.5, 37.9)	15.00 (10.9, 21.9)	60.25 (26,3, 72.0)	47.90 (28.7, 77.9)	36.00 (25.0, 47.0)	28.50 (24.6, 48.0)	47.00 (10.9, 80.0)
Height (cm) at baseline										
n	3	6	6	8	9	8	14	2	5	61
Mean (SD)	165.3 (10.50)	160.3 (5.85)	167.2 (14.73)	128.0 (11.19)	99.0 (11.74)	163.9 (13.11)	159.4 (8.44)	137.5 (17.68)	130.6 (8.14)	145.0 (25.83)
Median (Min, Max)	165.0 (155, 176)	160.0 (151, 167)	171.0 (140, 179)	132.5 (110, 140)	102.0 (80, 114)	165.5 (138, 179)	160.0 (143, 175)	137.5 (125, 150)	127.0 (123, 144)	155.0 (80, 179)
BMI (kg/m^2) at baseline										
n	3	6	6	8	9	8	14	2	5	61
Mean (SD)	23.00 (7.331)	21.09 (2.634)	18.73 (4.029)	17.14 (3.074)	16.16 (1.357)	20.99 (3.943)	20.11 (4.782)	18.44 (3.457)	18.76 (4.972)	19.19 (4.170)
Median (Min, Max)	23.66 (15.4, 30.0)	20.91 (17.4, 24.8)	19.43 (13.8, 25.0)	16.83 (13.6, 21.8)	16.62 (13.8, 17.8)	21.88 (13.8, 25.6)	18.16 (14.0, 30.2)	18.44 (16.0, 20.9)	16.74 (15.6, 27.5)	18.08 (13.6, 30.2)

[a] Phase 2 DL= 45 mg QD for patients weighing ≥ 45 kg, 30 mg QD for patients weighing ≥ 30 and < 45 kg, 15◦mg QD for patients weighing ≥ 15 to < 30◦kg and 5◦mg QD for patients weighing ≥ 5 to < 15◦kg

[b] Phase 1 Cohort 1 DL1 = 20 mg QD for patients weighing ≥ 45 kg and 15 mg QD for patients weighing ≥ 30 and < 45 kg

[c] Phase 1 Cohort 1 DL2 = 30 mg QD for patients weighing ≥ 45 kg and 20 mg QD for patients weighing ≥ 30 and < 45 kg

[d] Phase 1 Cohort 1 DL3 = 45 mg QD for patients weighing ≥ 45 kg and 30 mg QD for patients weighing ≥ 30 and < 45 kg

[e] Phase 1 Cohort 2 DL1= 45 mg QD for patients weighing ≥ 45 kg, 30 mg QD for patients weighing ≥ 30 and < 45 kg, 15◦mg QD for patients weighing ≥ 15 to < 30◦kg and 5◦mg QD for patients weighing ≥ 5 to < 15◦kg

[f] Including 1 CP-CML female patient (7 years old, race not reported, ethnicity: not Hispanic or Latino, body weight: 17.5 kg, height at baseline: 110 cm, BMI at baseline: 14.46 kg/m^2)

[g] Phase 1 Cohort 3 DL1= 45 mg QD for patients weighing ≥ 45 kg and 30 mg QD for patients weighing ≥ 30 and < 45 kg, 15◦mg QD for patients weighing ≥ 15 to < 30◦kg and 5◦mg QD for patients weighing ≥ 5 to < 15◦kg

Source: INCB 84344-102 CSR 11AUG2025 (cut off date 25JAN2025)

Table 14: Overall Extent of Exposure: Ponatinib Safety Population (paediatric patients; N=61)

Variable	Phase 1					Phase 2[a]				Total (N = 61)
	Cohort 1 (≥ 12 to < 18 years)			Cohort 2 (≥ 6 to < 12 years)	Cohort 3 (≥ 1 to < 6 years)	Cohort 1 (≥ 12 to < 18 years)		Cohort 2 (≥ 6 to < 12 years)		
	DL 1[b] (N = 3)	DL 2[c] (N = 6)	DL 3[d] (N = 6)	DL 1[e] (N = 8[f])	DL 1[g] (N = 9)	CP-CML (N = 8)	Other Tumors (N = 14)	CP-CML (N = 2)	Other Tumors (N = 5)	
Duration of ponatinib treatment (days)										
n	3	6	6	8	9	8	14	2	5	61
Mean (SD)	611.7 (978.95)	43.5 (29.26)	57.8 (41.68)	168.1 (288.07)	43.6 (55.51)	568.9 (394.09)	140.4 (194.22)	441.0 (202.23)	47.6 (29.97)	193.7 (329.91)
Median	57.0	28.5	44.0	60.0	28.0	533.0	81.0	441.0	33.0	60.0
Min-Max	36-1742	22-98	27-134	14-864	17-191	72-1100	8-765	298-584	18-86	8-1742
Average daily dose (mg)										
n	3	6	6	8	9	8	14	2	5	61
Mean (SD)	18.27 (2.837)	30.00 (0.000)	42.50 (6.124)	22.50 (8.018)	10.59 (5.228)	37.63 (10.351)	38.82 (9.101)	30.00 (21.213)	24.05 (13.500)	29.34 (13.400)
Median	19.82	30.00	45.00	22.50	15.00	40.59	45.00	30.00	17.67	30.00
Min-Max	15.0-20.0	30.0-30.0	30.0-45.0	15.0-30.0	5.0-15.0	15.0-45.0	15.0-45.0	15.0-45.0	12.6-45.0	5.0-45.0
Total reported dose (mg)										
n	3	6	6	8	9	8	14	2	5	61
Mean (SD)	12070 (19453.24)	1305.0 (877.67)	2267.5 (1197.91)	3168.8 (4402.54)	536.7 (881.91)	21513.8 (14914.22)	5394.6 (7554.58)	15375 (15422.00)	978.0 (414.93)	6083.6 (10278.15)
Median	1140.0	855.0	1980.0	1095.0	255.0	23985.0	2422.5	15375.0	1080.0	1380.0
Min-Max	540-34530	660-2940	1215-4020	240-12960	95-2865	2895-40590	360-28980	4470-26280	270-1290	95-40590

[a] Phase 2 DL = 45 mg QD for patients weighing ≥ 45 kg, 30 mg QD for patients weighing ≥ 30 and < 45 kg, 15◦mg QD for patients weighing ≥ 15 to < 30◦kg and 5◦mg QD for patients weighing ≥ 5 to < 15◦kg

[b] Phase 1 cohort 1 DL1 = 20 mg QD for patients weighing ≥ 45 kg and 15 mg QD for patients weighing ≥ 30 and < 45 kg

[c] Phase 1 cohort 1 DL2 = 30 mg QD for patients weighing ≥ 45 kg and 20 mg QD for patients weighing ≥ 30 and < 45 kg

[d] Phase 1 cohort 1 DL3 = 45 mg QD for patients weighing ≥ 45 kg and 30 mg QD for patients weighing ≥ 30 and < 45 kg

[e] Phase 1 cohort 2 DL1 = 45 mg QD for patients weighing ≥ 45 kg, 30 mg QD for patients weighing ≥ 30 and < 45 kg, 15◦mg QD for patients weighing ≥ 15 to < 30◦kg and 5◦mg QD for patients weighing ≥ 5 to < 15◦kg

[f] Including 1 CP-CML patient with duration of ponatinib treatment: 864 days, average daily dose of 15 mg and total reported dose of 12960 mg

[g] Phase 1 cohort 3 DL1 = 45 mg QD for patients weighing ≥ 45 kg and 30 mg QD for patients weighing ≥ 30 and < 45 kg, 15◦mg QD for patients weighing ≥ 15 to < 30◦kg and 5◦mg QD for patients weighing ≥ 5 to < 15◦kg

Source: INCB 84344-102 CSR 11AUG2025 (cut off date 25JAN2025)

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Efficacy and safety of ponatinib have been established in 2 clinical studies in the relevant target population for a total of 731 adult patients with RI CML and Ph+ ALL (AP24534-10-201 [phase 2, PACE] and AP24534-14-203 [phase 2, OPTIC]).

One pivotal study (phase 3, Ponatinib-3001 [PhALLCON]) and 2 supportive studies (phase 2, AP24534-11-001 [MDACC 2011-0030] and phase 2, INCB 84344-201 [GIMEMA LAL1811]) assessing the efficacy and safety of ponatinib as 1L therapy in adult patients with Ph+ ALL have been conducted. These 3 studies assessed the efficacy and safety of ponatinib as 1L treatment in patients with Ph+ ALL except for adult patients in study AP24534-11-001 who had been previously treated for Ph+ALL or CML (in accelerated phase or blast phase). A total of 294 adult patients have received ponatinib through these studies.

One study (phase 1/2, INCB 84344-102) assessing the efficacy and safety of ponatinib monotherapy for the treatment of recurrent or refractory leukemias or solid tumors in paediatric patients has been conducted. A total of 61 paediatric patients have received ponatinib monotherapy through this study including 11 CP-CML patients.

The below Table 15 lists the important exclusion criteria that were used to define the population in the 2 studies with RI CML and Ph+ALL adult patients (AP24534-10-201 and AP24534-14-203), the pivotal study assessing the efficacy and safety of ponatinib as 1L therapy in adult Ph+ALL in combination with chemotherapy (Ponatinib-3001) and in the paediatric study INCB 84344-102.

Table 15: Important exclusion criteria in pivotal studies in the development program

Criteria	**Reason for exclusion**	**Is it considered to be included as missing information?**	**Rationale** *(if not included as missing information)*
Pregnant or breastfeeding women	In nonclinical studies, embryo-fetal toxicities were observed. Toxicity studies in pregnant rats demonstrated fetal malformations (multiple soft tissue and skeletal alterations, as well as differences in the number of ossification site averages) at dose levels of 1 mg/kg/day and embryo-fetal toxicity [mortality (4%), decreased body weight gain and decreased food consumption; included increased post-implantation loss (early, late and total resorptions); reduced body weight; gross external alterations; multiple soft tissue and skeletal alterations, as well as differences in the number of ossification site averages] at dose levels of 3 mg/kg/day.	No	The SmPC includes warnings and advice for women of childbearing potential and men being treated with ponatinib. This risk is being appropriately managed and there are no plans to investigate this safety concern further. Teratogenicity is currently an important potential risk, which needs further characterization.
Significant or active cardiac disease	Based on the known class effects from other TKIs on cardiac function, patients with an increased baseline risk were excluded as a precautionary measure in order to reduce the risk of condition's aggravation.	No	Cardiac diseases are well known ponatinib adverse reactions that are described in the SmPC. No further characterization of this exclusion criteria as part of the pharmacovigilance plan is planned. VOEs are established ponatinib identified risks and the assessment of the cardiovascular status prior to start of therapy and the situations where an alternative treatment may be considered are addressed in the SmPC.

Criteria	**Reason for exclusion**	**Is it considered to be included as missing information?**	**Rationale** *(if not included as missing information)*
Patients taking medicinal products that are known to be associated with prolongation of the QT interval or Torsades de Pointes	Based on the known class effects from other TKIs on QTc intervals and the possible association with ponatinib, medications that are known to be associated with QT/ Torsades de Pointes were excluded in the clinical trial as a precautionary measure in order to reduce the risk of potentiated pharmacodynamic effets.	No	No further evaluation in the pharmacovigilance plan is considered warranted. Studies conducted to date demonstrated a lack of causal relationship. Also, the risk of QT prolongation is considered to be adequately communicated in the product information and it is expected to be managed during therapy as part of standard clinical practice.
Autologous or allogeneic stem cell transplant < 60-90 days prior to enrollment; any evidence of on-going GVHD, or GVHD requiring immunosuppressive therapy	Ponatinib was shown to deplete lymphoid organs in animal studies and a myelosuppressive effect is discussed for the class of TKIs. Patients were required to have recovered from stem cell transplants and not to be immune suppressed before initiating ponatinib as a precautionary measure in order to prevent the risk of potentiated pharmacodynamic effets with immunosuppressants.	No	No further characterization of this exclusion criteria as part of the pharmacovigilance plan is considered warranted as myelosuppression is a well known ponatinib adverse reaction and dose modifications for neutropenia that are unrelated to leukaemia are addressed in the SmPC.
Concurrent treatment with immunosuppressive agents, other than corticosteroids prescribed for a short course of therapy	Ponatinib was shown to deplete lymphoid organs in animal studies and a myelosuppressive effect is discussed for the class of TKIs. Concurrent use with immunosuppressive agents could potentially place patients at an increased risk. Since specific data on what the additive risk of treating	No	The safety and efficacy of concomitant administration of ponatinib and chemotherapy as well as corticosteroids was investigated in a phase 3 study (Ponatinib-

Criteria	**Reason for exclusion**	**Is it considered to be included as missing information?**	**Rationale** *(if not included as missing information)*
	patients with an immunosuppressive and ponatinib is unavailable, these agents were excluded in the clinical trial as a precautionary measure in order to reduce the risk of potentiated pharmacodynamic effects with immunosuppressants.		3001). No further characterization of this exclusion criteria as part of the pharmacovigilance plan is considered warranted as myelosuppression is a well known ponatinib adverse reaction and dose modifications for neutropenia that are unrelated to leukaemia are addressed in the SmPC.
Another primary malignancy within the past 3 years (except for nonmelanoma skin cancer or cervical cancer in situ)	Other malignancies were excluded because they might interfere with adequate evaluation of safety and efficacy.	No	Currently there is no plan for future pharmacovigilance activities to specifically further characterize this exclusion criterion. Physicians would likely not make treatment decisions with ponatinib based on whether a patient had a primary malignancy in the preceding three years.
Use of ponatinib in the treatment of patients with newly diagnosed CML	The objective of the Iclusig clinical development was to demonstrate the efficacy and safety of iclusig in patients with CP, AP, or BP chronic myeloid leukaemia who are resistant or intolerant to other TKIs (except for patients who have the T315I mutation).	No	Use of ponatinib in patients with newly diagnosed CML is outside of the approved indications for ponatinib.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 16: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	RI CML and Ph+ALL patients: The majority (78.5%) of enrolled patients were white. Asian and black/ African American patients account for 14.0% and 4.2%, respectively. 46.5 % of enrolled patients were from Europe and 31.7% were from North America (refer to Table 7). Newly-diagnosed Ph+ALL patients: In the pivotal phase 3 Ponatinib-3001 study, the majority (63.4%) of enrolled patients were white. Asian and Black/ African American patients account for 12.2% and 5.5%, respectively. 43.3% of enrolled patients were from Europe and 30.5% were from North America (refer to Table 11). No significant limitation was detected amongst patients of different ethnic origins, including the European population.

Subpopulations carrying relevant genetic polymorphisms	Mutations of BCR ABL are the main cause of development of resistance to therapy with imatinib. Ponatinib was specifically developed to overcome resistance through mutations of BCR ABL. The clinical studies demonstrated efficacy in patients with BCR ABL mutations including T315I mutation which causes resistance to all other authorized TKIs. Extensive non-clinical studies showed that ponatinib is mainly metabolized via CYP3A4/5. Several genetic polymorphisms have been described in the scientific literature for this cytochrome P450 subtype; however, a search of the scientific literature did not retrieve any articles indicating a polymorphism relevant for the metabolism of TKIs. Patients were not genotyped in the clinical trials.
Other: • Elderly	<u>RI CML and Ph+ALL patients:</u> Elderly patients (≥65 years) were well represented. 148 (20.2%) patients were > 65 to < 75 years of age and 43 (5.9%) patients were ≥ 75 years (refer to Table 7) <u>Newly-diagnosed Ph+ALL patients:</u> In the pivotal phase 3 Ponatinib-3001 study, 61 patients (37.2%) were ≥ 60 years of age (refer to Table 11).
• Paediatric patients	<u>Paediatric patients</u> Sixty-one peadiatric patients were exposed to ponatinib monotherapy including 9 aged ≥ 1 to < 6 years, 15 aged ≥ 6 to < 12 years and 37 aged ≥ 12 to < 18 years (see Table 13).

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 Post-Authorisation Exposure

On 14 DEC 2012, ponatinib was approved for marketing in the US by the FDA. On 01 JUL 2013, ponatinib received authorization to market ponatinib in the EEA via centralized procedure.

Ponatinib has been approved in 65 countries/regions as of 13 DEC 2025.

Worldwide exposure cumulatively since launch through 13 DEC 2025 is approximately 53,705 patient-years.

SV.1.1 Method Used to Calculate Exposure

Commercial Use

For ponatinib, the methodology used to calculate the exposure assumes an ADD of 30 mg.

The patient exposure can be estimated to be 19.58 million ADDs cumulatively, corresponding to approximately 53,705 patient-years of treatment cumulatively.

Estimated cumulative exposure is provided in Table 17.

SV.1.2 Exposure

Table 17: Estimated Patient Exposure of Ponatinib*

Country/Region	Cumulative Patient-years Since Launch
[α]EEA & UK & Switzerland	19,975
US & Canada	16,021
[§]Rest of World	17,709
Total	**53,705**

The figures presented are based on the shipping data for the countries below:
α- Austria, Belgium, Bulgaria, Croatia, Cyprus, The Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Malta, Netherlands, North Macedonia, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, and UK.
§- Australia, Argentina, Brazil, Chile, Colombia, Ecuador, Hong Kong, Indonesia, Israel, Japan, Republic of South Korea, Mexico, Malaysia, New Zealand, Peru, Philippines, Singapore, Taiwan, Province of China, Thailand, Turkiye and United Arab Emirates.
**As of 13 DEC 2025 (source: data on file)*

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Ponatinib has no addictive potential such as dependence and tolerance, thus the potential for misuse for illegal purposes is negligible.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

This section is not applicable as the RMP was already approved.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

This section is not applicable as the RMP was already approved.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Growth retardation is a new important potential risk.

Growth retardation data were reviewed as part of the procedure EMA/X/0000296489 to extend Iclusig indication to paediatric patients aged 6 years or older with CP-CML. A targeted literature search did not reveal the occurrence of growth retardation with ponatinib in paediatric patients. However, several articles mention the occurrence of growth retardation with first and second generation of BCR-ABL TKIs. In a non-clinical study with ponatinib, reductions in body weight gain were observed in juvenile rats but ponatinib did not adversely affect important developmental parameters. A cumulative review of growth retardation in the ponatinib clinical program and post-marketing experience revealed 3 cases with confounding factors, which are presented in Table 21. Considering that growth retardation is known to be associated with first and second generation of BCR-ABL TKIs and the limited non-clinical and clinical evidence regarding growth retardation and ponatinib, the MAH proposes to classify Growth retardation as an important potential risk (refer to Table 21).

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important identified and potential risks were selected based on their likelihood to have an impact on the risk-benefit balance of the product.

Table 18: Important Identified Risk: Serious Infections

Important Identified Risk	**Serious Infections***
Potential mechanism	Myelosuppression, which causes immune suppression.
Evidence source(s) and strength of evidence	Clinical studies and post-marketing data
Characterisation of the risk	**Clinical Trial Experience** **RI CML and Ph+ALL adult patients:** Serious infections were reported in 16.6% (121) of the study population (n=731). The most frequently reported serious infections were lower respiratory tract infections (pneumonia [5.5%], bronchitis and COVID-19 pneumonia [0.3% each] and atypical pneumonia, *Pneumocystis jirovecii* pneumonia, pneumonia fungal, pneumonia influenzal, pneumonia mycoplasmal, pneumonia respiratory syncytial viral, pneumonia staphylococcal [0.1% each]) followed by sepsis (sepsis [1.9%], bacteraemia [0.5%], septic shock [0.4%], klebsiella sepsis [0.3%], and abdominal sepsis, device related sepsis. neutropenic sepsis, staphylococcal bacteraemia and urosepsis [0.1% each]). Treatment-related serious infections were reported in 26 patients (3.6%). Grade 3 or 4 serious infections were reported in 100 patients (13.7%) and 21 patients (2.9%) had treatment-related Grade 3 or 4 serious infection. In 15 patients (2.1%), the serious infection was associated with a fatal outcome. Two patients had a fatal treatment-related serious infections (pneumonia and pneumonia fungal). OIs were reported in only 5 patients [0.7% of the study population (n= 731): herpes oesophagitis, oesophageal candidiasis, pneumonia fungal, pulmonary tuberculosis and *Pneumocystis jirovecii* pneumonia (1 patient each; 0.1%)]. OI could occur in this patient population, given their baseline diagnosis of advanced disease (AP-CML, BP-CML, CP-CML or Ph+ ALL) and associated blood cell decrease. **Newly-diagnosed Ph+ ALL adult patients:** Ponatinib-3001: Serious infections and infestations were reported in 27.6% (45) of the patients randomized in the ponatinib arm (n=163). The most frequently reported serious infections were COVID-19 (7 patients, 4.3%), septic shock (6 patients, 3.7%), sepsis (6 patients, 3.7%) and pneumonia (4 patients, 2.5%). Serious OIs were reported as follows: COVID-19 (7 patients, 4.3%), septic shock (6 patients, 3.7%), sepsis (6 patients, 3.7%), COVID-19 pneumonia (3 patients, 1.8%), bacteraemia (2 patients, 1.2%), kiebsiella sepsis (2 patients, 1.2), abdominal sepsis (1 patient, 0.6%), aspergillus infection (1 patient, 0.6%), clostridium colitis (1 patient, 0.6%), enterobacter infection (1 patient, 0.6%), mucormycosis (1 patient, 0.6%), neutropenic infection (1 patient, 0.6%), pseudomonal sepsis (1 patient, 0.6%), pseudomonas infection (1 patient, 0.6%) and stenotrophomonas bacteraemia (1 patient, 0.6%).

Important Identified Risk	Serious Infections*
	Fatal infections were reported in 6 patients (3.7%): septic shock (4 patients, 2.5%), abdominal sepsis (1 patient, 0.6%) and sepsis (1 patient, 0.6%). None were related to study drug. AP24534-11-001: Serious infections and infestations were reported in 55.2% (48) of the study population (n=87). The most frequently reported serious infections were pneumonia (20 patients; 23%), sepsis (14 patients; 16.1%), urinary tract infection (11 patients; 12.6%), infections and infestations – other (8 patients, 9.2%) and skin infection (6 patients; 6.9%). No opportunistic infection (OI) was reported. Two fatal TEAEs of sepsis (2 patients, 2.3%) were reported. None were related to study drug. INCB 84344-201: Serious infections and infestations were reported in 15.9% (7) of the study population (n=44): pneumonia (2 patients; 4.5%), bronchopulmonary aspergillosis (1 patient; 2.3%), enterococcal sepsis (1 patient; 2.3%), escherichia sepsis (1 patient; 2.3%), legionella infection (1 patient; 2.3%), septic shock (1 patient; 2.3%), staphylococcal infection (1 patient; 2.3%), staphylococcal sepsis (1 patient; 2.3%), urosepsis (1 patient; 2.3%). Serious OIs were reported as follows: bronchopulmonary aspergillosis (1 patient; 2.3%), enterococcal sepsis (1 patient; 2.3%), escherichia sepsis (1 patient; 2.3%), legionella infection, (1 patient; 2.3%), septic shock (1 patient; 2.3%), staphylococcal infection (1 patient; 2.3%), staphylococcal sepsis (1 patient; 2.3%) and urosepsis (1 patient; 2.3%). Fatal infections were reported in 4 patients (9.1%): bronchopulmonary aspergillosis (1 patient; 2.3%), pneumonia (2 patients; 4.5%) and septic shock (1 patient; 2.3%). None were related to study drug. **Paediatric patients:** Serious infections and infestations were reported in 8.2% (5) of the overall study population (n=61), including COVID-19 pneumonia, pneumonia, respiratory tract infection, sepsis and skin infection. Two serious OIs were reported: COVID-19 pneumonia and sepsis. One fatal infection of COVID-19 pneumonia was reported and considered not related to ponatinib by the investigator. None of the serious infections and infestations were reported in the CP-CML patients.

Important Identified Risk	Serious Infections*
	Post-marketing Experience Cumulatively, through 13 December 2025, 2,186 serious events were received. The most frequently reported serious infection events (≥20) were pneumonia (n=517), sepsis (n=217), infection (n=199), urinary tract infection (n=185), COVID-19 (n=181), nasopharyngitis (n=149), influenza (n=132), septic shock (n=84), upper respiratory tract infection (n=71), sinusitis (n=67), bronchitis (n=64), cellulitis (n=57), herpes zoster (n=52), bacteraemia (n=45), clostridium difficile infection (n=35), fungal infection (n=33), cystitis (n=32), viral infection (n=32), staphylococcal infection (n=29), device related infection (n=25), conjunctivitis (n=24), localized infection (n=24), clostridium difficile colitis (n=22), pneumonia fungal (n=22), respiratory tract infection (n=22) and bacterial infection (n=21). The most common serious infection events with a fatal outcome included pneumonia (n=76), sepsis (n=73), septic shock (n=50), infection (n=23), COVID-19 (n=14), fungal infection (n=7), neutropenic sepsis (n=5), pneumonia aspiration (n=5), staphylococcal sepsis (n=4), aspergillus infection (n=3), bacterial sepsis (n=3), cellulitis (n=3), COVID-19 pneumonia (n=3), mucormycosis (n=3), pneumonia fungal (n=3), staphylococcal bacteraemia (n=3), and pneumonia bacterial (n=3). The other events were reported with a frequency of 2 or less.
Risk factors and risk groups	Patients with leukemias typically acquire common infections due to the underlying hematologic condition. With active treatment, particularly those agents that cause defects in cell-mediated immunity, the incidence of opportunistic infections increases, although endogenous bacterial, mycobacterial, and fungal infections also occur (Young 2011).
Preventability	Infections related to immune suppression may occur. Dose adjustments for the myelosuppresion events that may place patients at increased risk of infection are provided in the proposed SmPC.
Impact on the risk-benefit balance of the product	The overall benefit-risk balance for ponatinib remains favourable when used in accordance with the SmPC.
Public health impact	Based on the review of published literature and clinical studies there is no immediate safety concern arising from severe infections.
*Risk described using pooled clinical data from AP24534-10-201 (phase 2, PACE , 06FEB2017) and AP24534-14-203 (phase 2, OPTIC, 15MAY2024) studies for RI CML and Ph+ALL adult patients, clinical trial data from Ponatinib 3001 (DLP: 12AUG2022), AP24534-11-001 (DLP: 14DEC2020) and INCB 84344-201 (DLP: 30SEP2021) studies for newly-diagnosed Ph+ALL adult patients, clinical trial data from INCB 84344-102 (DLP: 25JAN2025) study for paediatric patients and 13DEC2025 post-marketing data (source: data on file).	

Table 19: Important Identified Risk: Vascular Occlusion Events

Important Identified risk	Vascular occlusion events*
Potential mechanism	**A Potential Mechanism for BCR-ABLI-Associated VOEs** As outlined by Douxfils et al (2016), it is becoming evident that the BCR-ABL TKIs are associated with VOEs. Although the clinical manifestations of VOEs differ in severity and anatomical location (e.g. cardiac, cerebral, and peripheral), a common aspect of their action is their inhibition of ABL1 and ARG. ABL1 is critical for vascular development and integrity. A review of the literature of the downstream effectors that may mediate the vascular role has identified Rho, ROCK1, and ROCK2. Rho and ROCK in particular have been shown to mediate most of the vascular side effects seen with BCR-ABL TKIs: hypertension, angina, acute coronary syndrome, stroke, and pulmonary hypertension. Therapeutic inhibitors of ROCK exist and have a role in the treatment of cardiovascular disorders, including statins and fasudil [reviewed in (Dong et al 2010)]. Ponatinib did not increase the incidence or severity of arterial neointimal formation in response to flow-mediated changes induced by partial carotid artery ligation in mice when compared to animals administered vehicle. The lack of findings in this study suggest that ponatinib may not work through the ROCK pathway mechanism. No particular potential mechanism has been identified at this time except for Retinal Occlusive Events: **Retinal Vascular Events and Vision Loss:** As with other BCR-ABL TKIs, ponatinib inhibits a number of kinase pathways, including KIT and members of the FGFR, PDGFR, and VEGFR families of kinases. A review of ocular toxicities of targeted therapies proposes several mechanisms for various types of toxicities that may apply to ponatinib (Renouf et al 2012). The BCR-ABL inhibitors such as imatinib, dasatinib, and nilotinib are associated with periorbital edema, which can occur in up to 30% of patients. The mechanism proposed is the inhibition of c-KIT and PDGFR, with the effect being increased capillary permeability. Inhibitors of the VEGF pathway are used to treat ocular disorders such as diabetic retinopathy, with intravitreal injection being the preferred route of administration. This mode of administration has led to ocular toxicity, including ocular inflammation; however, few toxicities are reported with systemic use of these agents. The more-common pathway to retinal toxicities with these agents is suggested to be the risk of hypertension, which can lead to hypertensive retinopathy and also to the risk of other ocular toxicities, including emboli and occlusions.
Evidence source(s) and strength of evidence	Clinical studies and post-marketing data
Characterisation of the risk:	**<u>Clinical Trial Experience</u>** **RI CML and Ph+ALL adult patients:** **AOEs:** Cumulatively, 139 patients (19.0%) of the study population (n=731) were reported to have at least 1 AOE, and 111 patients

Important Identified risk	Vascular occlusion events*
	(15.2%) had at least 1 AOE reported to be an SAE. Treatment-related AOEs were reported in 94 patients (12.9%), and serious treatment-related AOEs were reported in 79 patients (10.8%). The most commonly reported AOE (ie, in >3% of the patients overall) was angina pectoris (30 patients; 4.1%), and a majority of those cases were reported to be Grade 1 or 2. Of the 139 patients with AOEs, 88 patients (12.0%) had Grade 3 or 4 events, 62 patients (8.5%) had Grade 3 or 4 treatment-related events, and 7 patients (1.0%) had Grade 5 AOEs (8 events) including acute MI, MI, myocardial ischaemia, CVA, peripheral ischemia, cerebral ischemia, hemorrhagic cerebral infarction, and mesenteric arterial occlusion (1 patient each; 0.1%). Three patients (0.4%) had related fatal AOEs (acute MI, MI and mesenteric arterial occlusion). In Cohort A (n=94) of Study AP24534-14-203 (phase 2, OPTIC), in which CP-CML patients receiving ponatinib starting dose of 45 mg had their daily dose reduced to 15 mg when ≤1% BCR-ABL1^{IS} was achieved, 13 patients (13.8%) were reported to have at least 1 AOE, 8 patients (8.5%) had serious AOEs. Treatment-related AOEs were reported in 10 patients (10.6%), and serious treatment-related AOEs were reported in 6 patients (6.4%). Grade 3 or 4 AOEs were reported in 6 patients (6.4%) and 6 patients (6.4%) had Grade 3 or 4 treatment-related AOEs. Two patients (2.1%) had fatal AOEs, 1 patient had a fatal treatment-related AOE (myocardial infarction). **Cardiac AOEs:** Cumulatively 67 patients (9.2%) of the study population (n=731), were reported to have at least 1 cardiac AOE, and 52 patients (7.1%) had at least 1 cardiac AOE reported to be an SAE. Treatment-related cardiac AOEs were reported in 43 patients (5.9%), and serious treatment-related cardiac AOEs were reported in 38 patients (5.2%). As was the case with AOEs in general, the most commonly reported cardiac AOE (ie, in > 3% of the patients overall) was angina pectoris (30 patients; 4.1%). Of the 67 patients with cardiac AOEs, 39 patients (5.3%) had Grade 3 or 4 events and 29 patients (4.0%) had Grade 3 or 4 treatment-related events. Coronary artery disease (1.5%) and myocardial infarction (1.2%) were the most frequently reported Grade 3 or 4 events. Three patients were reported to have a fatal cardiac AOE (acute MI, MI and myocardial ischaemia). In Cohort A (n=94) of Study AP24534-14-203 (phase 2, OPTIC), 5 patients (5.3%) were reported to have at least 1 cardiac AOE. Grade 3 or 4 cardiac AOEs were reported in 2 patients (2.1%). Two patients (2.1%) had fatal cardiac AOEs, 1 patient had a fatal treatment-related AOE (myocardial infarction). **Cerebral AOEs:** Cumulatively 53 patients (7.3%) of the study population (n=731), were reported to have at least 1 cerebral AOE, and 42 patients (5.7%) had at least 1 cerebral AOE reported to be an SAE. Treatment-related cerebral AOEs were reported in 33 patients (4.5%), and serious treatment-related cerebral AOEs were reported in 27

Important Identified risk	Vascular occlusion events*
	patients (3.7%). The events reported at the highest incidence were CVA and cerebral infarction, in 10 patients (1.4%). Of the 53 patients with cerebral AOEs, 30 patients (4.1%) had Grade 3 or 4 events and 22 (3.0%) had Grade 3 or Grade 4 treatment-related events. Cerebral infarction and carotid artery stenosis/occulsion were reported predominately as Grade 3 or 4 in severity (9 patients [1.2%] and 5 patients [0.7%], respectively). Fatal cerebral AOEs were reported in 3 patients (0.4%), including 1 patient each with CVA, cerebral ischemia, and hemorrhagic cerebral infarction. In Cohort A (n=94) of Study AP24534-14-203 (phase 2, OPTIC), 4 patients (4.3%) were reported to have at least 1 cerebral AOE. Grade 3 or 4 cerebral AOEs were reported in 2 patients (2.1%). Fatal cerebral AOEs were not reported. **Peripheral Vascular AOEs:** Cumulatively 61 patients (8.3%) of the study population (n=731), were reported to have at least 1 peripheral vascular AOE, and 43 patients (5.9%) had at least 1 peripheral vascular AOE reported to be an SAE. Treatment related peripheral vascular AOEs were reported in 39 patients (5.3%), and serious treatment-related peripheral vascular AOEs were reported in 30 patients (4.1%). The event reported at the highest incidence was peripheral arterial occlusive disease, in 22 patients (3.0%). Of the 61 patients with peripheral vascular AOEs, 35 patients (4.8%) had Grade 3 or 4 events and 23 (3.1%) had Grade 3 or 4 treatment-related events. Peripheral arterial occlusive disease was reported predominately as Grade 3 or 4 in severity (14 patients [1.9%]). Fatal peripheral vascular AOEs were reported in 2 patients (0.3%), including 1 patient each with peripheral ischemia and mesenteric arterial occlusion. In Cohort A (n=94) of Study AP24534-14-203 (phase 2, OPTIC), 4 patients (4.3%) were reported to have at least 1 peripheral vascular AOE. Grade 3 or 4 peripheral vascular AOEs were reported in 2 patients (2.1%). Fatal peripheral vascular AOEs were not reported. **VTEs:** Cumulatively 30 patients (4.1%) of the study population (n=731), were reported to have at least 1 VTE, and 25 patients (3.4%) had at least 1 VTE reported to be an SAE. Treatment related VTEs were reported in 14 patients (1.9%), and serious treatment-related VTEs were reported in 10 patients (1.4%). The event reported at the highest incidence was deep vein thrombosis in 10 patients (1.4%). Of the 30 patients with VTEs, 18 patients (2.5%) had Grade 3 or 4 events and 8 patients (1.1%) had Grade 3 or 4 treatment related events. Pulmonary embolism and deep vein thrombosis were reported predominately as Grade 3 or 4 in severity (7 patients [1.0%] and 5 patients [0.7%], respectively). Fatal VTEs were reported in 1 patient (0.1 %, pulmonary embolism; not related to Study drug).

Important Identified risk	Vascular occlusion events*
	In Cohort A (n=94) of Study AP24534-14-203 (phase 2, OPTIC), 1 patient (1.1%) had a VTE of retinal vein occlusion (Grade 1). **Retinal Vein Thrombotic Events and Vision Loss:** Cumulatively, 8 patients (1.1%) were reported to have at least 1 retinal VTE: 4 patients (0.5%) with retinal vein occlusion including 1 patient with Grade 3, 3 patients (0.4%; all Grade 3-4) with retinal vein thrombosis and 1 patient (0.1%) with retinal artery occlusion Grade 4. In Cohort A (n=94) of Study AP24534-14-203 (phase 2, OPTIC, 1 patient had retinal vein occlusion Grade 1. **Newly-diagnosed Ph+ ALL adult patients:** Ponatinib-3001: **AOEs:** Overall, 4 patients (2.5%) randomized in the ponatinib arm (n=163) experienced TE-AOEs (acute myocardial infarction, angina pectoris, lacunar infarction and peripheral arterial occlusive disease [1 patient each, 0.6%]. Treatment related TE-AOEs were reported in 3 patients (1.8%), and serious treatment-related TE-AOEs were reported in 2 patients (1.2%). Patients who experienced TE-AOEs were on study for a median of 26.5 days (range: 8-802 days) until the first AOE was observed. The exposure-adjusted rate per 100 person-years for TE-AOEs was 2.70 (95% CI: 0.04, 5.37) with a total person‑years of 147.95. Two patients experienced serious TE-AOEs. These events (acute myocardial infarction and angina pectoris) were assessed as Grade 3 and considered related to study drug. Grade 3 or 4 TE-AOEs were reported in 2 patients (1.2%). No fatal (Grade 5) TE-AOEs occurred. **VTEs:** Overall, 19 patients (11.7%) randomized in the ponatinib arm (n=163) experienced TE-VTEs. Treatment related TE-VTEs were reported in 8 patients (4.9%), and serious treatment-related TE-VTEs were reported in 2 patients (1.2%). The median time to onset of the first VTE was 71 days (range: 5-666 days). The exposure-adjusted rate per 100 person-years for TE-VTEs was 14.03 (95% CI: 7.35, 20.72) with a total person‑years of 135.39. The most common TE-VTEs (≥◦3 patients) were deep vein thrombosis (7 patients, 4.3%), embolism (3 patients, 1.8%) and superficial vein thrombosis (3 patients, 1.8%). Of the 19 patients that experienced TE-VTEs, 8 had events assessed as related to the use of PICC lines CVC for delivery of chemotherapy.

Important Identified risk	Vascular occlusion events*
	Serious TE-VTEs occurred in 3 patients (1.8%). Two patients had serious treatment-related TE-VTEs (both were pulmonary embolism). Grade 3 or 4 TE-VTEs were reported in 6 patients (3.7%). No fatal (Grade 5) TE-VTEs occurred. AP24534-11-001: **AOEs:** Overall, TE-AOEs occurred in 12◦patients (13.8%) of the study population (n=87), of which 8 (9.2%) had TE-AOEs that were related to treatment, and 3 (3.4%) had treatment-related TE-AOEs that were Grade◦≥◦3. The median number of days to when the first TE-AOE was observed was approximately 56 days (range: 4-1690◦days). The exposure-adjusted rate per 100 person-years for TE-AOEs was 7.89 (95% CI: 3.16, 12.63) with a total person-years of 152.00. The most common TE-AOEs by PT (≥◦2 patients) were angina pectoris (7 patients, 8%) and MI (4 patients, 4.6%). Of the 8◦patients (9.2%) with TE-AOEs related to treatment, the most common TE-AOEs by PT were angina pectoris (4◦patients, 4.6%), followed by MI (3◦patients, 3.4%) and acute coronary syndrome and transient ischaemic attack (1◦patient, 1.1% each). Serious TE-AOEs occurred in 5◦patients (5.7%), 4 patients (4.6%) had serious TE-AOEs that were reported as treatment-related, and 1◦patient (1.1%) had serious treatment-related TE-AOEs that were Grade◦≥◦3. Grade 3 or 4 TE-AOEs occurred in 4◦patients (angina pectoris, 1 patient and MI, 3◦patients) and a Grade 5 AOE occurred in 1 patient (MI). **VTEs:** Overall, TE-VTEs occurred in 11◦patients (12.6%) of the study population (n=87), of which 8 (9.2%) had a VTE that was considered related to treatment and 2 (2.3%) had treatment-related TE-VTEs that were Grade ≥◦3. The median number of days to when the first TE-VTE was observed in patients was approximately 79 days. The exposure-adjusted rate per 100 person-years for TE-VTEs was 7.63 (95% CI: 2.71, 12.55) with a total person-years of 144.21. The only TE-VTEs by PT were embolism (10◦patients, 11.5%) and thrombophlebitis superficial (1 patient, 1.1%). Under the PT of embolism, the reported terms were deep vein thrombosis (7 patients), embolism (3 participants), pulmonary embolism (2 patients), renal vein thrombosis (1 patient), and both deep vein thrombosis and pulmonary embolism (1◦patient). The occurrence of thrombophlebitis superficial was considered treatment-related and there were 7◦patients (8.0%) with treatment-related TE-VTEs of embolism. Study-drug related treatment-emergent VTEs under the PT of embolism were deep vein thrombosis

Important Identified risk	Vascular occlusion events*
	(5◦patients), embolism (3 patients), renal vein thrombosis (1◦patient), and pulmonary embolism (1 patient). Serious TE-VTEs occurred in 6◦patients (6.9%), 4◦patients (4.6%) had serious TE-VTEs that were reported as treatment-related, and 2◦patients (2.3%) had serious treatment-related TE-VTEs that were Grade◦≥◦3. Grade◦3 or 4 VTEs occurred in 4◦patients with embolism. No patients had Grade 5 VTEs. INCB 84344-201: A total of 15 patients (34.1%) of the study population (n=44) had a TE-VOE. Events in the Cardiac disorders and General disorders and administration site conditions SOCs were most common (11.4% each), and the most frequently reported PTs (≥ 2 patients) were chest pain (5 patients), acute coronary syndrome (3 patients), arterial occlusive disease (2 patients), and embolism (2 patients). Ten participants had 15 TE-VOEs related to treatment, and the most common (≥ 2 patients) treatment-related TE-VOEs by PT were acute coronary syndrome, arterial occlusive disease, and embolism. Serious TE-VOEs were reported in 10 patients (22.7%): acute coronary syndrome (3 patients), arterial occlusive disease (2 patients), and vascular graft occlusion, carotid artery stenosis, peripheral arterial occlusive disease, cerebrovascular accident, embolism, transient ischemic attack, peripheral ischemia, myocardial ischemia, myocardial infarction, and thrombosis (1 patient each). All serious TE-VOEs, except for the transient ischemic attack and myocardial infarction, were considered by the investigator to be related to ponatinib. Overall, Grade 3 TE-VOEs were reported in 5 patients (11.4%) and Grade 4 TE-VOEs were reported in 4 partients (9.1%). The following Grade 3 TE-VOEs were reported: acute coronary syndrome (3 partients, 6.8%), arterial occlusive disease (2 patients, 4.5%), and carotid artery stenosis, peripheral ischemia, and peripheral arterial occlusive disease (1 patient each, 2.3% each). The following Grade 4 TE-VOEs were each reported in 1 patient (2.3%): myocardial ischemia, vascular graft occlusion, cerebrovascular accident, and embolism. There were no fatal TE-VOEs during the study reporting period; 1 fatal TE−VOE (acute coronary syndrome) occurred more than 30 days after the participant discontinued ponatinib. **Paediatric patients:** In the overall pediatric population (n=61), 1 participant (1.6%) had an event of non-cardiac chest pain that met the protocol-defined criteria for AOEs. The participant had metastatic Ewing sarcoma. The event was serious, of Grade 2 in severity, and was assessed by the investigator as not related to ponatinib treatment. The event led to

Important Identified risk	Vascular occlusion events*

treatment interruption and was resolved after 3 days of onset. No VTEs were reported.

No protocol-defined AOEs nor VTEs were reported in the CP-CML patients.

Post-marketing experience

Number of Post-marketing VOEs Reported Over Different PBRER Intervals and Reporting Rates

PSUR period	PBRER 14 Dec 2015 - 13 Jun 2016	PBRER 14 Jun 2016 - 13 Dec 2016	PBRER 14 Dec 2016 - 13 Dec 2017			PBRER 14 Dec2017 – 13 Dec 2018		
			VOEs	AOEs	VTEs	VOEs	AOEs	VTEs
VOEs post-marketing (n)	108	101	188	147	41	226	191	35
Patient exposure	762.3	1037.0	1965	1965	1965	2816	2816	2816
Reporting rate	0.14	0.10	0.09	0.07	0.02	0.08	0.07	0.01

PSUR period	PBRER 14 Dec 2018 - 13 Dec 2019			PBRER 14 Dec 2019 - 13 Dec 2020			PBRER 14 Dec 2020 - 13 Dec 2021		
	VOEs	AOEs	VTEs	VOEs	AOEs	VTEs	VOEs	AOEs	VTEs
VOEs post-marketing (n)	298	248	50	271	223	48	233	211	22
Patient exposure	3747	3747	3747	5832	5832	5832	4850	4850	4850
Reporting rate	0.08	0.07	0.01	0.04	0.038	0.008	0.048	0.043	0.004

PSUR period	PBRER 14 Dec 2021 - 13 Dec 2022	PBRER 14 Dec 2022 - 13 Dec 2023	PBRER 14 Dec 2023 - 13 Dec 2024

<table>
<tr><td>Important Identified risk</td><td>Vascular occlusion events*
<table>
<tr><th></th><th>VOEs</th><th>AOEs</th><th>VTEs</th><th>VOEs</th><th>AOEs</th><th>VTEs</th><th>VOEs</th><th>AOEs</th><th>VTEs</th></tr>
<tr><td>VOEs post-marketing (n)</td><td>191</td><td>179</td><td>12</td><td>238</td><td>226</td><td>12</td><td>212</td><td>232</td><td>11</td></tr>
<tr><td>Patient exposure</td><td>6225</td><td>6225</td><td>6225</td><td>7199</td><td>7199</td><td>7199</td><td>7917</td><td>7917</td><td>7917</td></tr>
<tr><td>Reporting rate</td><td>0.030</td><td>0.028</td><td>0.001</td><td>0.033</td><td>0.031</td><td>0.001</td><td>0.027</td><td>0.029</td><td>0.001</td></tr>
</table>
<table>
<tr><th rowspan="2">PSUR period</th><th colspan="3">PBRER
14 Dec 2024 -13 Dec 2025</th></tr>
<tr><th>VOEs</th><th>AOEs</th><th>VTEs</th></tr>
<tr><td>VOEs post-marketing (n)</td><td>225</td><td>207</td><td>18</td></tr>
<tr><td>Patient exposure</td><td>8812</td><td>8812</td><td>8812</td></tr>
<tr><td>Reporting rate</td><td>0.026</td><td>0.023</td><td>0.002</td></tr>
</table>
Post-marketing data and clinical data continues to be consistent and cumulatively does not provide any new safety concerns.</td></tr>
<tr><td>Risk factors and risk groups</td><td>Risk factors for each category of vascular occlusion are given below, and include prior history of an event, hypertension, diabetes, smoking, hypercholesterolemia, and family history. A study suggests that the generation of NETs may be a mechanism by which cancers are prothrombotic (Demers et al 2012). NETs are associated with bacterial killing (Brinkmann et al 2004) and more recently, with thrombotic processes (Fuchs et al 2010, Brill et al 2012). The authors demonstrated that neutrophils from mice with CML-like myeloproliferative neoplasia generated NETs in vivo. When neutrophils were isolated and stimulated in vitro with platelet-activating factor, they generated NETs to a degree higher than would be predicted by the percentage of BCR-ABL1+ neutrophils, with in vitro imatinib or dasatinib having no effect on the rate of NET formation. The authors suggest that some systemic aspect of CML may be stimulating NET formation. If true, it suggests that CML itself is prothrombotic, and the property may not be sensitive to TKIs.
VOEs, especially AOEs, have also emerged as important identified risks associated with the use of other TKIs, including dasatinib and nilotinib (Valent et al 2014, Douxfils et al 2016).
AOEs were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia. Patients with and without cardiovascular risk factors, including patients aged 50 years or younger, experienced AOEs.</td></tr>
</table>

Important Identified risk	Vascular occlusion events*
	In Study AP24534-14-203 (phase 2, OPTIC), the majority of the 27 patients who were reported to have treatment-emergent AOE were ≥ 50 years old (19/27 patients; 70.4%) including twelve patients (44.4%) aged 50-64 years, 6 patients (22.2%) aged 65-74 years and 1 patient (3.7%) aged ≥ 75 years. More than half were female (18/27 patients; 66.7%). Nine patients (33.3%) reported a history of hypertension, none reported a history of ischaemic disease or nonischaemic cardiac disease, 1 (3.7%) reported a history of diabetes, 4 (14.8%) reported a history of obesity, 5 (18.5%) reported a history of hypercholesterolaemia and 10 (37%) reported a prior history of smoking. Similar ratios are observed in cohort A (45 mg). **AOEs:** **Cardiac AOEs:** Risk factors that promote heart disease include economic transition, urbanization, industrialization, and globalization. Therefore lifestyle changes promote heart disease. Further general risk factors include tobacco use, physical inactivity, and unhealthy diet. Newly emerging CVD risk factors such as low birth weight, folate deficiency and infestations are more frequent among the poorest in low- and middle-income countries (The National Academies. Promoting Cardiovascular Health in the Developing World (2010). Elderly patients and patients with underlying pre-disposing disease such as diabetes mellitus seemed to be at higher risk of developing ischaemic cardiac side effects during TKI therapy. **Cerebral AOEs:** Risk factors include heart disease (eg, atrial fibrillation, valvular disease, recent MI (Wein and Bornstein 2000; Di Tullio and Homma 2002), hypertension (MacMahon et al 1990), smoking (Kawachi et al 1993), diabetes (Karapanayiotides et al 2004), and hypercholesterolemia). Previous transient ischemic attack is a strong predictor of future stroke. **Peripheral Vascular AOEs:** Risk factors contributing to PVD include individuals who are ≥ 50 years of age with diabetes mellitus, smoking >10 pack-year/history of smoking (Hirsch et al 2001). PVD is more prevalent among families with atherosclerosis and in those with risk factors for cardiovascular disease, men, and certain ethnic populations. Many risk factors of PVD are similar to those that are associated with coronary atherosclerosis and include smoking, hypertension, diabetes, hyperlipidemia, homocysteinemia, metabolic syndrome, including inflammatory mediators (Selvin and Erlinger 2004; Smith et al 2004; Murabito 1997). About 90% of patients with renal artery stenosis have atherosclerosis as a predisposing factor; 10% of patients with renal artery stenosis have fibromuscular dysplasia as a predisposing factor. Atherosclerotic renal artery stenosis is a common condition that typically occurs in patients at high risk of cardiovascular disease with coexistent vascular disease at non- renal sites (Cheung et al 2005).

Important Identified risk	Vascular occlusion events*
	VTEs: VTEs were observed in the course of therapy. The possible reasons include active malignancy or acquired risk factors that may occur in the course of therapy, including immobility, trauma, surgery, and hospitalization, all of which exacerbate blood stasis in a hyperviscous state such as an active malignancy. Ku et al (2009) studied risk factors among patients with acute leukemia. They found that the 2-year incidence of venous thromboembolism in 2482 patients with ALL was 4.5%. Blann and Dunmore (2011) found an association of both arterial and venous thrombosis with various types of cancer. In study AP24534-14-203 (phase 2, OPTIC), only 3 patients (1.1%) overall experienced a TE-VTE and all resulted in study drug discontinuation. Events included retinal vein occlusion (Grade 1), pulmonary embolism (Grade 5) and retinal vein thrombosis (Grade 4) in Cohorts A, B and C, respectively. **Retinal Vascular Occlusive Events and Vision Loss:** Risk factors for BRVO and CRVO include the following (risk factors may differ for each type of occlusion): hypertension, cardiovascular disease, age, diabetes, smoking, obesity, glaucoma, retinal arteriolar abnormalities, and certain ethnic populations (Rogers et al 2010, Cugati et al 2006, Rehak et al 2008, The Eye Disease Case-control Study Group 1993, The Eye Disease Case-control Study Group 1996).
Preventability	Patients with vascular occlusion events and respective risk factors should be monitored and managed according to standard medical practice. Patients with retinal vascular events and respective risk factors should be monitored and managed according to standard medical practice.
Impact on the risk-benefit balance of the product	The overall benefit-risk balance for ponatinib remains favourable when used in accordance with the proposed SmPC. Based on the review of published literature and clinical studies, there is no immediate safety concern arising from TEAEs pertaining to category of retinal vascular events. The overall benefit-risk balance for ponatinib remains favourable when used in accordance with the SmPC.
Public health impact	Based on the review of published literature and clinical studies, there is no immediate safety concern arising from TEAEs pertaining to category of vascular occlusion events.

*Risk described using data from study AP24534-10-201 (phase 2, PACE 06FEB2017) and study AP24534-14-203 (phase 2, OPTIC, 15MAY2024) for RI CML and Ph+ALL adult patients, clinical trial data from Ponatinib 3001 (DLP: 12AUG2022), AP24534-11-001 (DLP: 14DEC2020), INCB 84344-201 (DLP: 30SEP2021) studies for newly-diagnosed Ph+ALL adult patients, clinical trial data from INCB 84344-102 (DLP: 25JAN2025) study for paediatric patients and 13DEC2025 post-marketing data (source: data on file).

Table 20: Important Potential Risk: Teratogenicity

Important Potential risk	**Teratogenicity**
Potential mechanism	No mechanism has been confirmed
Evidence source(s) and strength of evidence	Non-clinical studies
Characterisation of the risk	**Non-clinical Experience** Malformations were seen in animal studies. Toxicity studies in pregnant rats demonstrated fetal malformations (multiple soft tissue and skeletal alterations, as well as differences in the number of ossification site averages) at dose levels of 1 mg/kg/day and embryo-fetal toxicity (mortality (4%), decreased body weight gain and decreased food consumption; included increased postimplantation loss (early, late and total resorptions); reduced body weight; gross external alterations; multiple soft tissue and skeletal alterations, as well as differences in the number of ossification site averages) at dose levels of 3 mg/kg/day. Therefore strict contraception was required for all female patients of childbearing potential in clinical studies. **Clinical Experience** **RI CML and Ph+ALL adult patients:** In the study population (N= 731), 2 pregnancies were observed in female patients and 3 pregnancies were reported in partners of male patients of the study population. For one pregnancy with maternal exposure to ponatinib the pregnancy outcome was not reported and the other one resulted in elective abortion. The 3 pregnancies with paternal exposure resulted in live birth without complications/healthy infants. **Newly-diagnosed Ph+ ALL adult patients:** Ponatinib-3001 (ponatinib arm, n=163): One patient became pregnant approximately 2 months after initiating study treatment. Before enrolling in the study, the patient had a tubal ligation after her second pregnancy. The on-study pregnancy was an ectopic (tubal) pregnancy, and thus, was not viable. AP24534-11-001: During the study, pregnancy was not reported in any patient. INCB 84344-201: During the study, pregnancy was reported in 1 patient. The patient underwent an elective, induced abortion and continued ponatinib treatment. **Paediatric patients:** During the INCB84344-102 study (N=61), pregnancy was not reported in any paediatric patient.

Important Potential risk	**Teratogenicity**
	<u>Post-marketing Experience</u> Cumulatively, as of 13 December 2025, 218 events (73 serious and 145 non-serious) were received from 187 cases. The most frequently reported teratogenicity AEs (≥2) were pregnancy of partner (n=30), pregnancy (n=29), ichthyosis (n=24), maternal exposure during pregnancy (n=14), abortion spontaneous (n=11), gene mutation (n=9), cytogenetic abnormality (n=8), acquired gene mutation (n=8), exposure during pregnancy (n=7), foetal exposure during pregnancy (n=7), failure to thrive (n=6), congenital aplasia (n=5), Arnold-Chiari malformation (n=3), congenital megacolon (n=3), keratosis follicular (n=3), paternal exposure timing unspecified (n=3), tyrosine kinase mutation (n=3), abortion induced (n=2), Brugada syndrome (n=2), mastitis (n=2), and paternal exposure during pregnancy (n=2). The remaining events were reported with single frequency. Of the 187 reported cases 42 were maternal exposure, 43 were paternal exposure and 94 were non-pregnancy cases. Eight (8) of the reported 187 cases represented maternal & baby, paternal & baby or paternal and pregnant partner case reported for the same pregnancy event. The baby and pregnant partner cases from the same pregnancy were excluded from the assessment of pregnancy outcomes to avoid double counting. Outcome of maternal exposure (42): Among the maternal exposure cases, 7 cases reported delivery of a healthy infant, 3 cases reported neonates diagnosed with Congenital megacolon/Hirschsprung's disease, and 1 case reported a neonate diagnosed with Arnold–Chiari malformation. Thirteen (13) cases reported abortion (9 cases reported spontaneous abortion and 4 cases reported either induced abortion or abortion related to genetics), and the pregnancy outcome was unknown in 18 cases. Outcome of paternal exposure (43): Among the paternal exposure cases, 10 cases reported delivery of a healthy infant. Healthy delivery with no further details about the newborn was reported in 3 cases. One (1) case reported a fatal event of Patau's syndrome in the newborn, 1 case reported neonatal jaundice and 1 case reported neurodevelopmental disorder in the newborn (the reporting physician confirmed that the genetic disease was identified as transmitted from the mother, not related to ponatinib). Four (4) cases reported abortion (2 cases reported spontaneous abortion while 2 cases reported abortion related to genetics) and the pregnancy outcome was unknown in 23 cases.
Risk factors and risk groups	Women of childbearing potential
Preventability	Women of childbearing potential must use effective contraception during treatment with ponatinib. It is unknown whether ponatinib affects the effectiveness of systemic hormonal contraceptives. An alternative or additional method of contraception should be used. Ponatinib should be used during pregnancy only when clearly

Important Potential risk	Teratogenicity
	necessary. If it is used during pregnancy, the patient must be informed of the potential risk to the foetus.
Impact on the risk-benefit balance of the product	The overall benefit-risk balance for ponatinib remains favourable when used in accordance with the SmPC.
Public health impact	There is no significant impact to public health arising from teratogenicity, given the presence of recommended preventive actions applied, to exclude pregnancy immediately prior to and during ponatinib therapy.

*Risk described using pooled clinical data from AP24534-10-201 (phase 2, PACE , 06FEB2017) and AP24534-14-203 (phase 2, OPTIC, 15MAY2024) for RI CML and Ph+ALL adult patients, clinical trial data from Ponatinib 3001 (DLP: 12AUG2022), AP24534-11-001 (DLP: 14DEC2020) and INCB 84344-201(DLP: 30SEP2021) studies for newly-diagnosed Ph+ALL adult patients, clinical trial data from INCB 84344-102 (DLP: 25JAN2025) study for paediatric patients and 13DEC2025 post-marketing data (source: data on file).

Table 21: Important Potential Risk: Growth retardation

Important Potential risk	Growth retardation
Potential mechanism	No mechanism has been confirmed. The exact mechanism underlying growth failure with BCR-ABL TKI treatment is unclear. Deceleration of longitudinal growth in children on TKIs is possibly due to changes in bone mineral and vitamin D metabolism as well as alteration of the growth hormone–insulin-like growth factor 1 hormonal axis (Samis et al 2016, Phillips et al 2021, Cai et al 2023)
Evidence source(s) and strength of evidence	Growth impairment has been reported with first and second generation of BCR-ABL TKIs, however, its severity by TKI type has not been fully analyzed (Shima et al 2023).
Characterisation of the risk	**Non-clinical Experience** A juvenile toxicity study was conducted in rats to assess relative sensitivity of young versus mature animals to adverse effects of ponatinib, both before and after weaning, followed by a 4-week recovery period. Oral administration of ponatinib 3 mg/kg/day to juvenile rats, beginning PPD 15, resulted in mortality related to inflammatory effects within 6 to 7 days of treatment initiation. This high sensitivity of juvenile rats to ponatinib's overt toxic effects was likely a result of unexpectedly high plasma ponatinib concentrations after the first dose and stands in contrast to toxicity results in adult rats. Ponatinib exposures on PPD 35 in animals administered 0.75 or 1.5 mg/kg/day were appreciably lower than those determined on PPD 15. Administration of 0.75 and 1.5 mg/kg/day ponatinib from PPD 15 to 35 caused adverse reductions in body weight gain during preweaning and early postweaning treatment phases. These reductions were recovered during posttreatment PPD 35 to 63. Importantly, despite clear evidence of overt toxicity and adverse effects on body weight gain in juvenile rats, no adverse effects of

Important Potential risk	Growth retardation
	ponatinib on juvenile rat developmental parameters (vaginal opening, preputial separation, or bone measurements) were observed. Based on the occurrence of adverse body weight changes at all dose levels, a NOAEL of ponatinib in juvenile rats was not identified. However, the NOAEL on key developmental endpoints was 1.5 mg/kg/day. **Clinical Experience** **Paediatric patients:** Cumulatively as of 26FEB2026, 2 patients experienced Growth retardation in Study INCB84344-102 (N=63). One case occurred in a child treated with ponatinib 45 mg daily for low-grade glioma (pilocytic astrocytoma). The patient was growing according to normal growth curve until 2 months after ponatinib initiation. The patient's concurrent medical conditions of low-grade glioma and long period of secondary amenorrhea treated with choriongonadotropin, menotropin and ganirelix were highlighted as confounding factors. In response to the event, ponatinib dose was decreased to 30 mg daily. The second case occurred in a child treated with ponatinib 45 mg daily for CML-like Ph+ ALL. Slower growth was noted during previous intense ALL treatment. Previous treatment included chemotherapy in association with imatinib followed by dasatinib. Growth suppression was evidenced during study cycle 6 day 1. Puberty coinciding with the start of ponatinib treatment was also reported as a confounding factor. No action was taken with ponatinib in response to the event. **Post-marketing Experience** Cumulatively as of 26FEB2026, one post-marketing event of Growth retardation was reported. The case was a literature report (Nickel et al 2015) and concerned a child diagnosed with CP-CML. The child was first treated with imatinib. Twenty-four months after his diagnosis, the patient was treated with ponatinib 45 mg daily. After 18 months, the dose of ponatinib was reduced to 15 mg daily. The child experienced decline in height velocity. The authors highlighted that imatinib has been associated with growth impairment and ponatinib may also impair growth based on the patient's growth curve. However, it did not prevent pubertal development. Ponatinib was well tolerated and provided excellent disease control. No action was taken with ponatinib. The 2 cases described in the paediatric Study INCB 84344-102 and the one post-marketing case reported as of 26FEB2026 have confounding factors including the concurrent medical conditions and/or previous use of first and second generation TKIs. Long-term

Important Potential risk	Growth retardation
	effect on growth and development is monitored as part of Study INCB 84344-102.
Risk factors and risk groups	The effects on growth were seen mainly in prepubertal patients (Samis et al 2016).
Preventability	Monitoring of growth should be performed in paediatric patients under ponatinib treatment.
Impact on the risk-benefit balance of the product	The overall benefit-risk balance for ponatinib remains favourable when used in accordance with the SmPC.
Public health impact	Based on the review of published literature, clinical study and post-marketing data, the public health impact is unknown.

*Risk described using clinical trial data from Study INCB 84344-102 and post-marketing data as of 26FEB2026 (source: data on file).

SVII.3.2 Presentation of the Missing Information

Not applicable.

PART II: MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Table 22: Summary of Safety Concerns

Summary of safety concerns	

Important identified risks	Serious Infections
	Vascular occlusion events, comprising:
	• Arterial Occlusive Events (AOEs)
	  ○ Cardiac Arterial Occlusive events
	  ○ Cerebral Arterial Occlusive events
	  ○ Peripheral Vascular Arterial Occlusive events
	  ○ Retinal Arterial Occlusive events and Vision Loss
	• Venous Thrombotic/Embolic Events (VTEs)
	  ○ Retinal Vein Thrombotic events and Vision Loss

Important potential risks	Teratogenicity Growth retardation
Missing information	None

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

There are currently no specific adverse reaction follow-up questionnaires being used for ponatinib.

Other forms of routine pharmacovigilance activities:

There are no other forms of routine pharmacovigilance acitivities ongoing for ponatinib.

III.2 Additional Pharmacovigilance Activities

None.

The following studies imposed for primarily efficacy reasons have safety secondary objectives:

Ponatinib-3001 (PhALLCON) summary:

Ponatinib-3001 (PhALLCON): A Phase 3, Randomized, Open label, Multicenter Study Comparing Ponatinib Versus Imatinib, Administered in Combination With Reduced- Intensity Chemotherapy, in Patients With Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

Secondary safety objectives:

The safety objectives are:

To characterize the rates of AEs/SAEs, AOEs, VTEs, and other safety outcomes of interest in the 2 cohorts, using multiple methods.

To compare the tolerability between the 2 cohorts, including the rates of discontinuation, dose reductions, and dose interruptions due to AEs.

Safety concerns addressed by the study: VOEs

Size of the safety database in the study: 163 patients exposed to ponatinib and 81 patients exposed to imatinib.

Safety interim reports milestones:

Final study report due: DEC 2028.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 23: 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 authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance ativities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Table 24: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies that are conditions of the marketing authorisation				
Ponatinib-3001 (PhALLCON): A Phase 3, Randomized, Open label, Multicenter Study Comparing Ponatinib Versus Imatinib, Administered in Combination With Reduced- Intensity Chemotherapy, in Patients With Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL) Ongoing	The primary objective of the study was to compare the efficacy of ponatinib versus imatinib, administered as first-line therapy in combination with reduced-intensity chemotherapy, in patients with newly diagnosed Ph+ ALL, as measured by the MRD-negative CR rate at the end of induction The key secondary objective was to compare EFS between the 2 cohorts.	Long term efficacy	Final report	DEC 2028

PART V RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 Routine Risk Minimisation Measures

Table 25: Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Serious Infections	Routine risk communication: SmPC section 4.8 PL section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond Product Information: None
Vascular occlusion events • Arterial Occlusive Events (AOEs) o Cardiac Arterial Occlusive events o Cerebral Arterial Occlusive events o Peripheral Vascular Arterial Occlusive events o Retinal Arterial Occlusive events and Vision Loss • Venous Thrombotic/Embolic Events (VTEs) Retinal Vein Thrombotic events and Vision Loss	Routine risk communication: SmPC section 4.2, 4.4 and 4.8 PL section 2, 3 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Interruption for arterial occlusion and venous thromboembolism in SmPC section 4.2 and PL section 3. Reducing the dose to 15mg should be considered for CP-CML adult patients who have achieved molecular response (MR2 i.e. ≤1% BCR-ABL1^{IS}) and to the recommended reduced dose based on patient's weight for CP-CML paediatric patients who have achieved a molecular response in SmPC section 4.2. Guidance before starting treatment with ponatinib with regards to the assessment of the cardiovascular status of the patient and the management and monitoring of the cardiovascular risk factors in SmPC section 4.2 and 4.4. Description of the arterial occlusion events, risk factors, dose dependency, time to onset, contra-indications, and recommendation for monitoring for evidence of arterial occlusion and opthtalmic examination if decreased vision or blurred vision in SmPC section 4.4 and PL section 2. Other routine risk minimization measures beyond Product Information: None

Safety concern	Routine risk minimisation activities
Important potential risks	
Teratogenicity	Routine risk communication: SmPC section 4.6 and 5.3 PL section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendation for women to avoid becoming pregnant and for men to not father a child in SmPC section 4.6. Recommendation for women to avoid becoming pregnant and for men to not father a child in PL section 2. Other routine risk minimization measures beyond Product Information: None
Growth retardation	Routine risk communication: SmPC section 4.4 PL section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendation for close monitoring of growth in peadiatric patients under ponatinib treatment in SmPC section 4.4. Recommendation for close monitoring of growth in paediatric patients under ponatinib treatment in PL section 2. Other routine risk minimization measures beyond Product Information: None

V.2 Additional Risk Minimization Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimization Measures

Table 26: Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Important Identified Risks		
Safety concern	*Risk minimisation measures*	*Pharmacovigilance activities*
Serious Infections	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse

	SmPC section 4.8 and PL section 4. Additional risk minimisation measures: None	reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Vascular occlusion events • Arterial Occlusive Events o Cardiac Arterial Occlusive events o Cerebral Arterial Occlusive events o Peripheral Vascular Arterial Occlusive events o Retinal Arterial Occlusive events and Vision Loss • Venous Thrombotic/Embolic Events (VTE) o Retinal Vein Thrombotic events and Vision Loss	Routine risk minimisation measures: SmPC section 4.2 and PL section 3 contain advice for dose adjustment or interruption for arterial occlusion and venous thromboembolism. SmPC section 4.2 contains guidance on assessment of the cardiovascular status and the management and monitoring of the cardiovascular risk factors. SmPC Section 4.4 and PL Section 2 contain advice on monitoring and managing vascular occlusion events. SmPC section 4.8 and PL section 4. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Important Potential Risks		
Safety concern	*Risk minimisation measures*	*Pharmacovigilance activities*
Teratogenicity	Routine risk minimisation measures: SmPC section 4.6 and 5.3 PL section 2 Recommendation for women to avoid becoming pregnant and for men to not father a child in SmPC section 4.6 and PL section 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Growth retardation	Routine risk minimisation measures: SmPC section 4.4 PL section 2 Recommendation for close monitoring of growth in paediatric patients under ponatinib treatment in SmPC section 4.4 and PL section 2. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Part VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ICLUSIG (PONATINIB)

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

Iclusig's SmPC and its PL give essential information to HCPs and patients on how Iclusig should be used.

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

I THE MEDICINE AND WHAT IT IS USED FOR

Iclusig is authorised for use in adult patients with CML and Ph+ ALL and paediatric patients with CP-CML (see SmPC for the full indication). It contains Ponatinib as the active substance and it is given by either 45 mg, 30 mg or 15 mg film-coated tablets or 5 mg hard capsules filled with 10 round 0.5 mg film-coated tablets (mini-tablets) orally.

Further information about the evaluation of Iclusig’s benefits can be found in Iclusig’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/iclusig).

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- 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 minimise its risks.

Together, these measures constitute routine risk minimisation 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.

II.A List of Important Risks and Missing Information

Important risks of Iclusig are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Iclusig. 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 27: Lists of Important Risks and Missing Information

List of Important Risks and Missing Information	

Important identified risks	Serious Infections
	Vascular occlusion events, comprising:
	• Arterial Occlusive Events (AOEs)
	  o Cardiac Arterial Occlusive events
	  o Cerebral Arterial Occlusive events
	  o Peripheral Vascular Arterial Occlusive events
	  o Retinal Arterial Occlusive events and Vision Loss
	• Venous Thrombotic/Embolic Events (VTEs)
	  o Retinal Vein Thrombotic events and Vision Loss

Important potential risks	Teratogenicity Growth retardation
Missing information	None

II.B Summary of Important Risks

Table 28: Summary of Important Identified Risk Serious Infections

Important Identified Risk: Serious Infections	
Evidence for linking the risk to the medicine	Clinical studies and post-marketing data
Risk factors and risk groups	Patients with leukemias typically are affected by nuisance infections due to the underlying hematologic condition. With active treatment, particularly those agents that cause defects in cell-mediated immunity, the incidence of opportunistic infections increases, although endogenous bacterial, mycobacterial, and fungal infections also occur (Young, 2011).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8 and PL section 4. Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Table 29: Summary of Important Identified Risk Vascular Occlusion Events

Important Identified Risk: Vascular occlusion events	
Evidence for linking the risk to the medicine	Clinical studies and post-marketing data
Risk factors and risk groups	Risk factors for each category of vascular occlusion are given below, and include prior history of an event, hypertension, diabetes, smoking, hypercholesterolemia, and family history. A study suggests that the generation of NETs may be a mechanism by which cancers are prothrombotic (Demers et al 2012). NETs are associated with bacterial killing (Brinkmann et al 2004) and more recently, with thrombotic processes (Fuchs et al 2010, Brill et al 2012). The authors demonstrated that neutrophils from mice with CML-like myeloproliferative neoplasia generated NETs in vivo. When neutrophils were isolated and stimulated in vitro with platelet-activating factor, they generated NETs to a degree higher than would be predicted by the percentage of BCR-ABL1+ neutrophils, with in vitro imatinib or dasatinib having no effect on the rate of NET formation. The authors suggest that some systemic aspect of CML may be stimulating NET formation. If true, it suggests that CML itself is prothrombotic, and the property may not be sensitive to TKIs. VOEs, especially AOEs, have also emerged as important identified risks associated with the use of other TKIs, including dasatinib and nilotinib (Valent et al 2014, Douxfils et al 2016).

Important Identified Risk: Vascular occlusion events	
	AOEs were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia. Patients with and without cardiovascular risk factors, including patients aged 50 years or younger, experienced AOEs. In Study AP24534-14-203 (phase 2, OPTIC), the majority of the 27 patients who were reported to have treatment-emergent AOE were ≥ 50 years old (19/27 patients; 70.4%) including twelve patients (44.4%) aged 50-64 years, 6 patients (22.2%) aged 65-74 years and 1 patient (3.7%) aged ≥ 75 years. More than half were female (18/27 patients; 66.7%). Nine patients (33.3%) reported a history of hypertension, none reported a history of ischaemic disease or nonischaemic cardiac disease, 1 (3.7%) reported a history of diabetes, 4 (14.8%) reported a history of obesity, 5 (18.5%) reported a history of hypercholesterolaemia and 10 (37%) reported a prior history of smoking. Similar ratios are observed in cohort A (45 mg). **AOEs:** **Cardiac AOEs:** Risk factors that promote heart disease include economic transition, urbanization, industrialization, and globalization. Therefore lifestyle changes promote heart disease. Further general risk factors include tobacco use, physical inactivity, and unhealthy diet. Newly emerging CVD risk factors such as low birth weight, folate deficiency and infestations are more frequent among the poorest in low- and middle-income countries (The National Academies. Promoting Cardiovascular Health in the Developing World (2010). Elderly patients and patients with underlying pre-disposing disease such as diabetes mellitus seemed to be at higher risk of developing ischaemic cardiac side effects during TKI therapy. **Cerebral AOEs:** Risk factors include heart disease (eg, atrial fibrillation, valvular disease, recent MI (Wein and Bornstein 2000; Di Tullio and Homma 2002), hypertension (MacMahon et al 1990), smoking (Kawachi et al 1993), diabetes (Karapanayiotides et al 2004), and hypercholesterolemia). Previous transient ischemic attack is a strong predictor of future stroke. **Peripheral Vascular AOEs:** Risk factors contributing to PVD include individuals who are ≥ 50 years of age with diabetes mellitus, smoking >10 pack-year/history of smoking (Hirsch et al 2001). PVD is more prevalent among families with atherosclerosis and in those with risk factors for cardiovascular disease, men, and certain ethnic populations. Many risk factors of PVD are similar to those that are associated with coronary atherosclerosis and include smoking, hypertension, diabetes, hyperlipidemia, homocysteinemia, metabolic syndrome, including inflammatory mediators (Selvin and Erlinger 2004; Smith et al 2004; Murabito 1997).

Important Identified Risk: Vascular occlusion events	
	About 90% of patients with renal artery stenosis have atherosclerosis as a predisposing factor; 10% of patients with renal artery stenosis have fibromuscular dysplasia as a predisposing factor. Atherosclerotic renal artery stenosis is a common condition that typically occurs in patients at high risk of cardiovascular disease with coexistent vascular disease at non- renal sites (Cheung et al 2005). **VTEs:** VTEs were observed in the course of therapy. The possible reasons include active malignancy or acquired risk factors that may occur in the course of therapy, including immobility, trauma, surgery, and hospitalization, all of which exacerbate blood stasis in a hyperviscous state such as an active malignancy. Ku et al (2009) studied risk factors among patients with acute leukemia. They found that the 2-year incidence of venous thromboembolism in 2482 patients with ALL was 4.5%. Blann and Dunmore (2011) found an association of both arterial and venous thrombosis with various types of cancer. In study AP24534-14-203 (phase 2, OPTIC), only 3 patients (1.1%) overall experienced a TE-VTE and all resulted in study drug discontinuation. Events included retinal vein occlusion (Grade 1), pulmonary embolism (Grade 5) and retinal vein thrombosis (Grade 4) in Cohorts A, B and C, respectively. **Retinal Vascular Occlusive Events and Vision Loss:** Risk factors for BRVO and CRVO include the following (risk factors may differ for each type of occlusion): hypertension, cardiovascular disease, age, diabetes, smoking, obesity, glaucoma, retinal arteriolar abnormalities, and certain ethnic populations (Rogers et al 2010, Cugati et al 2006, Rehak et al 2008, The Eye Disease Case-control Study Group 1993, The Eye Disease Case-control Study Group 1996).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 and PL section 3 contain advice for dose adjustment or interruption for arterial occlusion and venous thromboembolism. SmPC section 4.2 contains guidance on assessment of the cardiovascular status and the management and monitoring of the cardiovascular risk factors. SmPC Section 4.4 and PL Section 2 contain advice on monitoring and managing vascular occlusion events. SmPC section 4.8 and PL section 4. Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

Table 30: Summary of Important Potential Risk Teratogenicity

Important Potential Risk: Teratogenicity	
Evidence for linking the risk to the medicine	Non-clinical studies
Risk factors and risk groups	Women of childbearing potential
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 and 5.3 PL section 2 Recommendation for women to avoid becoming pregnant and for men to not father a child in SmPC section 4.6 and PL section 2. Additional risk minimization measures: None
Additional pharmacovigilance activities	None

Table 31: Summary of Important Potential Risk Growth retardation

Important Potential Risk: Growth retardation	
Evidence for linking the risk to the medicine	Growth impairment has been reported with first and second generation of BCR-ABL TKIs, however, its severity by TKI type has not been fully analyzed (Shima et al 2023).
Risk factors and risk groups	The effects on growth were seen mainly in prepubertal patients (Samis et al 2016).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 PL section 2 Recommendation for close monitoring of growth in paediatric patients under ponatinib treatment in SmPC section 4.4 and PL section 2. Additional risk minimisation measures: None
Additional pharmacovigilance activities	None

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorisation:

Study short name: Ponatinib-3001 (PhALLCON)

Purpose of the study: The primary objective of the study was to compare the efficacy of ponatinib versus imatinib, administered as first-line therapy in combination with reduced-intensity chemotherapy, in patients with newly diagnosed Ph+ ALL, as measured by the MRD-negative CR rate at the end of induction. The key secondary objective was to compare EFS between the 2 cohorts.

II.C.2 Other Studies in Post-Authorisation Development Plan

None

PART VII ANNEXES

LIST OF ANNEXES

Pages 84-86 have been removed per EMA guidance on the preparation and redaction of risk management plans (body and annexes 4 and 6)

- ANNEX 1 EUDRAVIGILANCE INTERFACE
- ANNEX 2 TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME
- ANNEX 3 PROTOCOLS FOR PROPOSED, ONGOING, AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

Page 88 has been removed per EMA guidance on the preparation and redaction of risk management plans (body and annexes 4 and 6)

- ANNEX 5 PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP PART IV

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Not applicable

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

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Pages 95-103 have been removed per EMA guidance on the preparation and redaction of risk management plans (body and annexes 4 and 6)

- ANNEX 8 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Signature Page for [redacted]

Approval Task	[redacted] Approver PSR, [redacted] Global Risk Management & Safety Surveillance 17-Mar-2026 15:49:01 GMT+0000

Approval Task	Achint Kumar Approver Executive Director, QPPV 17-Mar-2026 16:13:05 GMT+0000

Signature Page for [redacted]