Amsterdam, 21 May 2026
EMADOC-1700519818-3228538
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Iclusig

International non-proprietary name: Ponatinib

Procedure No. EMA/X/0000296489

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
PD	Pharmacodynamics
PK	Pharmacokinetics
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk management plan
SmPC	Summary of product characteristics
1L	first-line
AAF	age-appropriate formulation
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AOE	arterial occlusive event
AP	accelerated phase
AST	aspartate aminotransferase
AUC0-∞	area under the steady-state plasma or serum concentration-time curve from Hour 0 to infinity
AUClast	area under the concentration-time curve from the first observed to the last measurable concentration
BCR-ABL1	breakpoint cluster region-Abelson
BCR-ABL1IS	BCR-ABL1 transcript level as measured by the International Scale
BP	blast phase
bw	body weight
CCyR	complete cytogenetic response
CHMP	Committee for Medicinal Products for Human Use
CHR	complete hematologic response
CI	confidence interval
Cmax	maximum concentration
CML	chronic myeloid leukemia
COVID-19	coronavirus disease 2019
CP	chronic phase
CR	complete response
CSR	Clinical Study Report
CV%	percent coefficient of variation
CyR	cytogenetic response
DLP	data lock point
DLT	dose-limiting toxicity
ECG	electrocardiogram
EMA	European Medicines Agency
EOT	end of treatment

EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase 3
GGT	gamma-glutamyl transferase
HSCT	hematopoietic stem cell transplantation
IA	interim analysis
MCyR	major cytogenetic response
MedDRA	Medical Dictionary for Regulatory Activities
MMR	major molecular response
MPAL	mixed phenotype acute leukemia
MR	molecular response
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NE	not evaluable
OS	overall survival
PD	pharmacodynamic(s)
PEG	polyethylene glycol
PFS	progression-free survival
Ph+	Philadelphia chromosome–positive
Ph-like	Philadelphia chromosome–like
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
popPK	population pharmacokinetic
PT	preferred term
PY	patient-years
QD	once daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia's formula
RMP	Risk Management Plan
RP2D	recommended Phase 2 dose
R/R	recurrent/refractory
RT-PCR	reverse transcriptase–polymerase chain reaction
RWD	real-world data
SmPC	Summary of Product Characteristics
SOC	system organ class
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
UK	United Kingdom
US	United States
VTE	venous thromboembolism

1. Administrative/regulatory information and recommendations on the procedure

1.1. Submission of the dossier

On 12 September 2025, Incyte Biosciences Distribution B.V. submitted a group of variations consisting of an extension of the marketing authorisation and the following variation:

Variation(s) requested		Type	Annexes affected
C.I.6.a	**Addition of a new indication**	**II**	**I, III and RMP**

The MAH applied for an extension application to introduce a new pharmaceutical form associated with a new strength (5 mg hard capsule) grouped with a type II variation (C.I.6.a) to add a new indication (to include treatment of paediatric patients aged 6 years and older with chronic phase chronic myeloid leukaemia (CP-CML) who are resistant or intolerant to at least one tyrosine kinase inhibitor), based on interim results from study INCB 84344-102, an ongoing open-label, single-arm, Phase 1/2 study evaluating the safety and efficacy of ponatinib monotherapy for the treatment of R/R leukemias, lymphomas, or solid tumors in paediatric participants.

As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.8, 5.1, 5.2, 6.1 and 6.5 of the SmPC are updated. Package Leaflet is updated accordingly. The RMP version 23.4 has also been submitted.

1.2. Legal basis

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008,(2) points (c) and (d) - Extensions of marketing authorisations.

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Iclusig was designated as an orphan medicinal product EU/3/09/715 and EU/3/09/716 on 02 February 2010 in the following conditions: Treatment of acute lymphoblastic leukaemia and Treatment of chronic myeloid leukaemia.

The orphan designations expired on 03 July 2023.

1.3. Scientific advice and protocol assistance

Not applicable.

1.4. Information on paediatrics

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMA/PE/0000266809 on the agreement of a paediatric investigation plan (PIP) for the treatment of chronic myeloid leukaemia.

At the time of submission of the application, the PIP EMA/PE/0000266809 had been completed.

The PDCO issued on 17 October 2025 a positive opinion on compliance for the PIP EMA/PE/0000266809.

All studies/measures contained in the PIP were checked for compliance:

Study No., identifier	Description
Study 5, study identifier not available	Development of capsules of 5 mg strength
Study 2, Study No. 902650	Toxicity study in juvenile rats
Study 1, study identifier not available	Development of an age-appropriate formulation for oral use
Study 3, Study INCB 84344-102	Open-label, single-agent, dose-escalation, multi-centre, trial to investigate tolerability, safety and activity of ponatinib in the paediatric population from 1 year to less than 18 years of age with malignant disease for which no effective treatment is known, and with an expansion cohort of the paediatric population with a chronic phase chronic myeloid leukaemia and other leukaemia and solid tumours
Study 4, Study Ponatinib-1501	Open-label, multi-centre trial including a safety lead-in phase to investigate the safety, the activity and the efficacy of ponatinib as add-on to standard therapy in the paediatric population from 1 year to less than 18 years of age with relapsed or refractory BCR-ABL translocation-positive ALL

1.5. Information on orphan market exclusivity

1.5.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH submitted a critical report addressing the possible similarity with authorised orphan medicinal products.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur:	Filip Josephson
Co-Rapporteur:	Ewa Balkowiec Iskra

The application was received by the EMA on	12 September 2025
The procedure started on	30 October 2025
The CHMP Rapporteur's first Assessment Report was received on	19 January 2026
The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur's report on	21 January 2026

The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report ad circulated to all PRAC and CHMP members on	27 January 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 February 2026
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	26 February 2026
The MAH submitted the responses to the CHMP consolidated List of Questions on	20 March 2026
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 April 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	07 May 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Iclusig 5mg capsules on	21 May 2026
The CHMP adopted a report on similarity of Iclusig with Scemblix (see Appendix on similarity)	21 May 2026

1.7. CHMP outcome

1.7.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.4. of this report.

In this procedure, the CHMP reviewed the available data from the studies conducted in accordance with the agreed PIP EMA/PE/0000266809, namely studies INCB 84344-102 and Ponatinib-1501. The results of these studies are reflected in sections: 4.1, 4.2, 4.8, 5.1 and 5.2 of the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet. Further, the results of study INCB 84344-102 were pivotal in supporting this application.

The paediatric age-appropriate formulation (5 mg hard capsules) is included in the SmPC as part of the present extension application.

The results from study 902650 (toxicity study in juvenile rats) were assessed in a previous procedure (EMEA/H/C/002695/II/0007) and a summary of the results was added to section 5.3 of the SmPC.

1.7.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.5. of this report.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Iclusig is not similar to Scemblix within the meaning of Article 3 of Commission Regulation (EC) No 847/2000. See the appendix on similarity.

1.7.3. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Iclusig 5 mg hard capsules as monotherapy for the treatment of paediatric patients 6 years of age or older with chronic phase chronic myeloid leukaemia (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, is favourable.

1.7.4. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

1.7.5. Official batch release

Not applicable

1.7.6. Other conditions and requirements of the marketing authorisation

1.7.6.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

1.7.7. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.7.7.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.7.8. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

2. These conditions fully reflect the advice received from the PRAC. Introduction

2.1. Therapeutic Context

In the EU, the incidence of chronic myeloid leukemia (CML) is reportedly 0.7/million/year at age between 1 and 14 years of age and increases to 1.2/million/year in adolescents (Meral Günes et al 2021).

The underlying cause of CML is the BCR-ABL fusion oncoprotein, which results from a reciprocal t(9;22) chromosomal translocation in hematopoietic stem cells. The presence of BCR-ABL is a requirement for diagnosis (Loghavi, 2024). The translocation leads to the fusion of the BCR coding sequence with the tyrosine kinase coding region of ABL. This fusion event results in the constitutive activation of ABL kinase activity. BCR-ABL activates multiple downstream pathways that contribute to the growth and survival of cells (Hazlehurst et al 2009).

CML is typically a triphasic continuum of disease with a chronic phase (CP-CML), accelerated phase (AP-CML), and blast phase (BP-CML); characteristics of the disease and prognosis are different for each phase. If transition to AP CML occurs, median survival is typically limited to less than 1 year, while patients in blast crisis (which resembles acute leukemia) usually live for only a few months.

There are some differences in the biology and clinical presentation of CML in paediatric and adult populations. Children often present with higher white blood cell counts, larger spleens relative to body size, and more aggressive clinical features (Hijiya et al 2016). Paediatric cases also show distinct BCR breakpoint patterns (Smith et al 2021) and different transcript type levels, which may translate into different responses to TKIs (Hijiya et al 2016).

On the other hand, paediatric and adult CML share a common disease etiology, characterized by the presence of the BCR-ABL1 fusion gene (Hijiya et al 2016). Diagnostic criteria for paediatric CML, including cytogenetic confirmation and molecular detection of BCR-ABL1 transcripts via RT-PCR, are aligned with those used in adults. Paediatric CML also shares key histopathological and clinical features with adults. Both populations typically present with hypercellular bone marrow exhibiting myeloid predominance and splenomegaly. The natural history of disease progression follows a similar trajectory across age groups (CP, AP, and BP) with comparable hematologic abnormalities and organ system involvement (Suttorp et al 2021). Disease classification also follows the same internationally accepted guidelines such as European LeukemiaNet (Senapati et al 2023).

Monitoring parameters, including hematologic response as well as cytologic (CyR) and molecular (MR) responses, such as major cytogenetic response (MCyR) and major molecular response (MMR), are similarly defined in paediatric and adult populations and are assessed using the same methodologies and thresholds, typically extrapolated from adult protocols due to limited paediatric-specific data (Hijiya et al 2016).

The introduction of treatment with imatinib, a first-generation TKI, dramatically improved the prognosis of children and adolescents with CML (Leoni and Biondi 2015, Suttorp et al 2011); nonetheless, the initial presence or the development of resistance to imatinib due to mutations in the kinase domain is a common cause of disease recurrence (Leoni and Biondi 2015, 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 including dasatinib, nilotinib and bosutinib are more potent inhibitors of native BCR ABL than imatinib and inhibit many, although not all, imatinib resistant BCR-ABL mutants (Cortes et al 2011, O'Hare et al 2007).

In the EU, imatinib, dasatinib, nilotinib, and bosutinib (for children aged 6 years and older) are approved for 1L treatment of paediatric CP CML. Dasatinib, nilotinib, and bosutinib (for children aged 6 years and older) are also approved as second-line treatment for paediatric CP-CML. However, dasatinib, nilotinib, and bosutinib are ineffective against the T315I BCR ABL mutant (Soverini et al 2014), which is present in 11% to 20% of adult patients resistant to imatinib (Cortes et al 2011, O'Hare et al 2007).

The currently approved TKIs for paediatric use are expected to have the same limitations of resistance to mutations as observed in adults. The incidence of resistant mutations in the paediatric population is unknown. Another challenge in BCR-ABL TKI treatment in paediatric patients is sustaining the therapeutic benefits while minimizing toxicities that can impact growth and that are also tolerated over decades of exposure (Hijiya et al 2016). Although there is evidence of the effect of imatinib on growth impairment (Hijiya et al 2016, Hijiya et al 2023), the long-term impact of chronic use of TKIs in children is not yet fully understood (Smith et al 2021).

2.2. Aspects of development

The original paediatric development plan for ponatinib was agreed upon with the EMA Paediatric Committee in July 2012 (EMEA-001186-PIP01-11) and has since undergone subsequent modifications, the most recent of which was approved in July 2025.

2.3. Description of the product

Ponatinib is a small-molecule TKI designed to inhibit BCR ABL1. Ponatinib inhibits both native BCR ABL1 and its mutant forms, including the T315I gatekeeper mutation that confers resistance to other approved TKIs that target BCR ABL1 (ie, imatinib, dasatinib, nilotinib, and bosutinib). Through direct inhibition of native BCR ABL1 and its variants, ponatinib inhibits aberrant downstream signaling by reducing phosphorylated crk-like protein, thereby promoting apoptosis and cell death in BCR ABL1–positive cells (O'Hare et al 2009).

Ponatinib received full approval in the EU on 01 July 2013 and in the US on 28 November 2016.

In the EU, ponatinib is indicated in adult patients with:

- chronic phase, accelerated phase, or blast phase 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
- Philadelphia chromosome-positive 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.

3. Quality aspects

Introduction

The finished product applied for in this line extension is presented as hard capsules containing 5 mg of ponatinib (as hydrochloride) as active substance. Each capsule contains 10 small film-coated tablets, each containing 0.5 mg of ponatinib.

Iclusig is currently available as film-coated tablets in three strengths (15 mg, 30 mg, 45 mg). This line

extension application concerns the addition of a lower strength suitable for doses that cannot be achieved by using the film-coated tablets and for paediatric patients who are unable to swallow tablets.

Other ingredients are: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal anhydrous silica and magnesium stearate in the tablet cores. The film-coating consists of talc, macrogol, poly(vinyl alcohol) and titanium dioxide (E171). The capsule shells contain hypromellose and titanium dioxide (E171).

The product is available in high density polyethylene (HDPE) bottles with screw-top closures, containing 30 capsules, together with one plastic canister containing a molecular sieve desiccant, as described in section 6.5 of the SmPC.

3.1. Active substance

The active substance is ponatinib, present as the hydrochloride salt. The active substance is the same as approved for the currently marketed presentations (film-coated tablets in the strengths 15 mg, 30 mg, and 45 mg). There are no changes to the active substance dossier sections as part of this line extension. An acceptable QP-declaration according to the EMA template for the active substance and intermediate manufacturing sites has been provided.

3.2. Finished medicinal product

3.2.1. Description of the product and pharmaceutical development

The finished product is a hard capsule provided in one strength, 5 mg, with each capsule containing 10 small film-coated tablets. The qualitative and quantitative composition of the finished product is provided. The applicant refers to the small film-coated tablets in the capsule as 'minitabs' or 'minitablets'. Where the term 'minitab' or 'minitablet' is used in this AR it means the content of the hard capsules.

All excipients are well known pharmaceutical ingredients, commonly used in solid dosage forms, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. There are no overages or overfills.

As indicated above, ponatinib is currently available as film-coated tablets in three strengths (15 mg, 30 mg, 45 mg). The present application concerns the addition of a lower strength suitable for lower dosing, and as an alternative for those not able to swallow intact tablets.

Coated minitablets in hard capsules were considered the best approach to combine palatability, flexible dosing, and easy administration. Salt form, polymorph, and physicochemical properties relevant for a solid, oral dosage form (aqueous solubility at different pHs, particle size, and stability) were discussed for the active substance.

The film-coated minitablets contain the same excipients as the commercial film-coated tablets. The qualitative composition of the minitablet is the same as that of the cores of the film-coated commercial tablets. Based on this, no incompatibility issues are expected.

During the procedure, a major objection (MO1) was raised as the development of the dissolution test method specific for the minitablet capsule formulation was not described. In response, the applicant provided the requested information. During development different apparatuses and stirring speeds were evaluated. The choice of apparatus, buffer type, and pH, is justified with reference to formulation

characteristics and active substance solubility properties. Investigations were made to demonstrate the dissolution method's discriminatory power. It was concluded that the dissolution test method development is appropriate and that the formulation is relatively robust to changes in manufacturing process or composition. The MO1 was resolved.

The capsules are intended to be swallowed whole, but for patients not able to do this the capsules can also be opened and the minitablets be sprinkled on food. Compatibility of the finished product with the proposed vehicles (water, apple juice, apple sauce and yogurt at room temperture) has been confirmed by studies.

The intended commercial product has the same film-coated minitablet formulation and the same white capsule shell as the clinical batches used in the BE study (containing titanium dioxide only, with no ink). For the initial registration batches, purple Colorista capsule shells were used. The Colorista shells were used to generate stability data to support potential future changes to the shell colour or adding printing (if desired). During the procedure, a major objection (MO2) was raised as there were differences in dissolution behaviour between the registration batches and the clinical batches which could not be regarded as similar. In response, the applicant conducted a set of studies to determine the reason for the differences in dissolution behaviour. The accumulated data – investigations of loose minitablets of registration batches and one clinical batch, minitablets from the registration batches re-encapsulated into white capsule shells, and minitablets from a clinical batch re-encapsulated into Colorista capsule shells – supported the applicant's conclusion that the differences were caused by the choice of capsule shells and not by any potential differences in tablet manufacturing process or properties of excipients. The studies also excluded that the colouring agents interfered with the analytical procedure. The applicant agreed to revert to the white capsules instead of the purple-coloured capsules for commercial production. This was supported and the MO2 was resolved.

The commercial pack for ponatinib capsules is a white, round, wide-mouth high-density polyethylene (HDPE) bottle, with a polypropylene two-piece closure induction seal liner. A 1 g packet with silica gel is included inside the HDPE bottle. The choice of HDPE bottles and desiccant is the same as currently used for the film-coated tablet presentations. A single bottle size of 40 cc was selected to accommodate the fill count and capsule size. For the HDPE, compliance with Commission regulation (EU) 10/2011, and also Ph. Eur. 3.1.3 and 3.15 are confirmed. Acceptable specifications are provided, together with drawings and Certificates of Analysis of the components of the primary packaging.

3.2.2. Manufacture of the product and process controls

Batch release is performed at Tjoapack Netherlands B.V., Nieuwe Donk 94879 AC Etten-Leur, Netherlands or Incyte Biosciences Distribution B.V., Paasheuvelweg 25, 1105 BP Amsterdam, Netherlands. Satisfactory proof of GMP compliance has been provided for all manufacturing sites.

The manufacturing process consists of a direct compression process followed by film coating and encapsulation. The process includes the following steps: dry blending, minitablet compression, aqueous film-coating, capsule shell weight sorting, encapsulation and final filled capsule weight sorting. The process is considered to be a standard manufacturing process. The commercial batch size isdefined.

The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

A plan for process validation to be performed at full manufacturing scale has been provided and considered acceptable. Compliance with the Note for Guidance on start of shelf-life of the finished product form (CPMP/QWP/072/96) is declared.

3.2.3. Product specification

The finished product specifications shown in Table 2 include appropriate tests for this kind of dosage form; visual description, identification (HPLC, UV), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), water content (Ph. Eur.), dissolution (USP, HPLC), microbiological examination (Ph. Eur.).

The justifications for limits/ranges for appearance, identity, assay, uniformity of dosage units, water content, and microbiological examination are acceptable. For related substances, the proposed limits are in line with ICH Q3B, as considering a maximum daily dose of 45 mg.

During the procedure, a major objection (MO3) was raised on the initial proposed dissolution limits, which was also relevant to two other major objections (MO1 & MO2) relating to dissolution test method development and dissolution behaviour of registration batches. In response, following the resolution of the two other MOs, the dissolution test limit was tightened and justified, based on the dissolution behaviour of relevant clinical batches. The MO was resolved.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

With respect to nitrosamines risk assessment, as the active substance and excipients are the same and the manufacturing process is similar to the already approved formulations, and as the additional factors specific to the minitablet capsule formulation (site generated water, capsule shells) have been assessed, it was concluded that there are no additional risks for the formation of nitrosamine impurities.

Batch release data for clinical batches and registration batches were provided. As discussed above, purple capsule shells were used for the registration batches instead of the white ones intended for commercial production and there was a notable difference in dissolution results for the clinical batches compared to the three registration batches. This was raised as a major objection (MO2), and resolved by provision of additional dissolution data and by the applicant reverting to the white capsule shells for commercial production. Results for other specification parameters were consistent and compliant with the proposed specification limits.

3.2.4. Stability of the product

The applicant submitted supportive stability data for one pilot scale batch of 5 mg capsules with the composition applied for marketing authorisation. These studies included stability data up to 60 months under long term storage conditions (25°C/60% RH) and 6-month under accelerated conditions (40°C/75% RH).

Appearance, assay, degradation products, and water content remained essentially unchanged during the course of the stability studies conducted on these supportive batches. For dissolution, all batches complied with the specification limit.

Stability data was provided for the three registration batches (with purple capsule shells) for 6 months at long term (25°C/60% RH), intermediate (30°C/65% RH), and accelerated (40°C/75% RH) storage conditions. All results complied with specifications but different dissolution behaviour were observed. As discussed above under MO2, this was attributed to the use of purple capsule shells.

Dissolution results for re-encapsulated tablets (from purple to white capsule shells) at 1 and 3 months (tablet age at re-encapsulation approximately 5 months, i.e., 8 months in the current study's 3-month point) were submitted. The re-encapsulation was performed as part of the investigations into the

dissolution behaviour differences between white and purple capsules discussed above. All results complied with specifications and dissolution was similar to that observed in the clinical batch.

The assessment of stability considered the completed long-term and accelerated stability studies on the supportive batches, the 6 months data for all storage conditions for the product in purple capsule shells, and the dissolution results for re-encapsulated tablets at 1 and 3 months, and the applicant's reference to ICH Q1C regarding amount of stability data expected for extensions.

Based on accumulated data provided, a 12 months shelf-life when stored in the original container with desiccant is considered acceptable.

3.2.5. Post-approval change management protocol(s)

Not applicable

3.2.6. Adventitious agents

With the exception of lactose monohydrate, none of the excipients used in the formulation of ponatinib hard capsules are of human or animal origin. A declaration confirming compliance with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 Rev 3) is provided for lactose monohydrate.

3.2.7. GMO

Not applicable

3.3. Discussion on chemical, pharmaceutical and biological aspects

No new information on the active substance has been presented in this line extension application. Information on development, manufacture and control of the finished product has been presented in a satisfactory manner.

The development of the 5 mg capsule formulation was based on experience gained from the currently marketed strengths of the 15 mg, 30 mg, and 45 mg film-coated tablets. During the procedure three MOs were raised relating to the development of the dissolution test method, differences observed in dissolution behaviour between clinical and registration batches and the proposed dissolution specification limits. The MOs were resolved by provision of additional development data, reverting to the white capsule shells used in the clinical batches and tightening the proposed dissolution limit.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

3.4. Conclusions on chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

3.5. Recommendations for future quality development

Not applicable.

4. Non-clinical aspects

No new clinical data have been submitted in this application.

4.1. Ecotoxicity/environmental risk assessment

The Applicant has planned to perform an OECD TG309 study, and if the persistence criterion is met they will also perform a OECD TG305 study. The relevant ERA studies in support of this application should have been provided prior to opinion. However, based on a national scientific advice, it was agreed that these studies should be available in October 2026 (OECD TG309) and June 2027 (OECD TG305, only if triggered by results of OECD TG309) respectively. When these studies are submitted, they should also be included in an updated ERA document where all the ERA data available are presented and discussed in accordance with the relevant guideline.

4.2. Overall discussion and conclusions on non-clinical aspects

4.2.1. Discussion

No new data have been submitted with this extension, which is considered acceptable.

Regarding the ERA, an OECD TG 309 study will be available October 2026 and an OECD TG305 study will be available in June 2027 (only if triggered by results of OECD TG309). When these studies are submitted, they should also be included in an updated ERA document where all the ERA data available are presented and discussed in accordance with the relevant guideline. The updated ERA should also include any change in PEC_{SW} as a consequence of the increased population.

4.2.2. Conclusions

No new non-clinical data have been submitted. This is considered acceptable.

An updated ERA with additional data will be submitted during 2026/2027.

There are no non-clinical objections to approval of this extension application.

5. Clinical aspects

5.1. Introduction

This application is intended to support the broadening of the currently approved indication for ponatinib for the treatment of CP-CML to include the paediatric patient population aged ≥6 years of age. The proposed approach to demonstrate positive B/R in the target population is based on a PK-bridging strategy.

Study INCB 84344-102 is the main paediatric clinical study supporting this submission, including paediatric patients in the target population (CML patients) and in other patient populations.

In addition, study Ponatinib-1501 (ponatinib in combination with chemotherapy in paediatric patients with Ph+ ALL) was also submitted and its results included in section 5.1 of the SmPC.

5.1.1. GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier.

5.1.2. Tabular overview of clinical trials

Table 3: Tabular overview of main clinical studies

Study	Objectives	Study design	Population	Treatments	PK sampling
INCB 84344-101	Compare the BA of ponatinib "enabling" capsule AAF to 15 mg tablet in fasted state Compare BA of intact "enabling" capsule AAF in fasted state to "enabling" capsule AAF opened and sprinkled on either yogurt or applesauce	Single-dose, open-label, randomized, 2-cohort crossover; 1-week between each period	Healthy adult participants aged: 18-55 years Cohort 1 = 16 participants Cohort 2 = 24 participants	Cohort 1, 2-period: 15 mg commercial tablet, PO, fasted [reference]; 3 × 5 mg "enabling" capsule intact, PO, fasted [test] Cohort 2, 3-period: 5 mg "enabling" capsule intact, PO, fasted [reference]; 5 mg capsule opened and sprinkled on yogurt, PO [test]; 5 mg "enabling" capsule opened and sprinkled on applesauce, PO [test]	Days 1, 8, 15 (Day 1, Cohort 2 only): Predose (0 h), 1, 2, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, 120 h postdose
INCB 84344-103	Compare BA of ponatinib Minitab capsule AAF to 15 mg	Single-dose, open-label, randomized, 2-cohort	Healthy adult participants aged: 18-55 years; Cohort 1	Cohort 1, 2-period: 15 mg commercial tablet, PO fasted	Days 1, 8, 15 (Day 1, Cohort 2 only): Predose (0 h), 1, 2, 4, 5,

	tablet in fasted state Compare BA of intact Minitab capsule AAF in fasted state to opened Minitab capsule AAF and sprinkled on either yogurt or applesauce	crossover; 1-week between each period	= 16 participants Cohort 2 = 24 participants	[reference]; 3 × 5 mg Minitab capsule intact, PO, fasted [test] Cohort 2, 3-period: 3 × 5 mg Minitab capsule intact, PO, fasted [reference]; 3 × 5 mg Minitab capsule opened and sprinkled on yogurt, PO [test]; 3 × 5 mg Minitab capsule opened and sprinkled on applesauce, PO [test]	6, 8, 12, 24, 36, 48, 72, 96, 120 h postdose
Study Ponatinib-1501	Evaluate the safety, tolerability, efficacy, and PK of ponatinib when administered in combination with multiagent chemotherapy in paediatric participants with Ph+ MPAL, or Ph-like ALL with targetable kinase activation lesions and who had relapsed or were refractory to prior BCR-ABL1 TKI or had a BCR-ABL1 T315I mutation	Open-label, single-arm, Phase ½ multicenter	Paediatric participants aged: ≥ 1 to ≤ 21 years	Cohort 1: 30 mg adult-equivalent dose: 30 mg tablet PO for participants ≥ 45 kg; 20 mg for participants ≥ 30 kg to < 45 kg Cohort 2: 15 mg adult-equivalent dose: 15 mg tablet or Minitab capsule PO for participants ≥ 45 kg; 10 mg for participants ≥ 30 kg to < 45 kg; 7.5 mg for participants ≥ 15 kg to < 30 kg; 5 mg to participants ≥ 5 kg to < 15 kg	Reinduction block Day 1: 1-2 h, 6-8 h, 24 h postdose participants < 20 kg; 1-2 h, 3-4 h, 6-8 h, 24 h postdose participants ≥ 20 kg Reinduction block Day 22: predose, 3-4 h 6-8 h participants < 20 kg; predose, 1-2 h, 3-4 h, 6-8 h postdose participants ≥ 20 kg
INCB 84344-102	Open-label, single-arm, Phase ½	Open-label, single-arm,	Paediatric participants aged: ≥ 1 to <	45 mg adult-equivalent dose of	Phase 1: Cycle 1 Day 8 predose, Cycle 1 Day 15

	multicenter trial evaluating safety, tolerability, efficacy, and PK of ponatinib for the treatment of recurrent or refractory leukemias or solid tumors in paediatric participants	Phase ½ multicenter	18 years Cohort 1: aged: ≥ 12 to < 18 years Cohort 2: aged: ≥ 6 to < 12 years Cohort 3: aged: ≥ 1 to < 6 years	tablet, powder-filled capsule ("enabling formulation") or Minitab capsule PO 5 mg for participants 5 kg to < 15 kg; 15 mg to participants ≥ 15 kg to < 30 kg; 30 mg to participants ≥ 30 kg to < 45 kg; 45 mg to participants ≥ 45kg	predose, 2 h (±15 min) postdose, 4 h (± 15 min) postdose, 8 h (± 30 min) postdose, Cycle 3 Day 1 predose Phase 2: Cycle 2 Day 1 predose, 3-4 h postdose, 6-8 h postdose

5.2. Clinical pharmacology

The clinical pharmacology data package of this extension application includes results from two clinical studies conducted in paediatric participants: Studies INCB 84344-102 and Ponatinib-1501. The package also includes two relative bioavailability studies conducted in healthy adult participants (Studies INCB 84344-101 and INCB 84344-103) to support the development of a new formulation (MiniTabs capsules) for the paediatric population.

5.2.1. Methods

5.2.1.1. Bioanalytical methods, Pharmacokinetics

Ponatinib concentrations in plasma collected from healthy adult participants (Studies INCB 84344-101 and INCB 84344-103) and paediatric participants (Study INCB 84344-102, Ponatinib-1501) were measured by a validated liquid chromatography-tandem mass spectrometry assay (LC/MS/MS).

The liquid chromatography-tandem mass spectrometry (LC-MS/MS) analytical method for the determination of ponatinib in human plasma was based on a previous method established suitable for analysis. The method was validated prior to and during study sample analysis.

In-study bioanalytical reports were included for Studies INCB 84344-101 and paediatric participants (Study INCB 84344-102) and Study Ponatinib-1501 as well as for study INCB 84344-103.

For studies with a submitted bioanalysis report, all clinical samples were analysed within the established stability period of the analyte. Overall, the determination of ponatinib in human plasma showed adequate performance. ISR assessments were conducted and met the acceptance criteria for all studies.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

The paediatric PopPK model is considered to have high impact for the benefit-risk assessment. The benefit-risk in paediatric patients ≥6 years is extrapolable from the adult population via PK bridging extrapolation of efficacy/safety from adults by means of exposure matching. The PK sampling design in the paediatric study was based on a sparse sampling scheme which means that non-compartmental analysis approaches are not relevant for analysing these data. Instead, the MAH proposed PopPK analysis including PopPK simulations which is an acceptable strategy as such. Furthermore, the PopPK simulations are considered highly important since the MAH has proposed a different posology than the studied posology in Study INCB84344-102.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population Pharmacokinetics

A paediatric PopPK model was developed based on PK data collected in the target population. The objectives were to develop a PopPK model with PK data collected in paediatric Study INCB 84344-102 and to perform simulations to inform the proposed posology.

A pooled paediatric+adult PopPK analysis was conducted. The dataset for PopPK analysis comprised PK data from four Phase 1 clinical studies in adult healthy volunteers (Studies AP24534-11-102, AP24534-11-103, AP24534-12-107, and AP24534-12-108), three Phase 1/2 and 3 studies in adult study participants with hematologic malignancies (Studies AP24534-07-101, AP24534-11-106, and AP24534-12-301) and one Phase 1/2 study in paediatric study participants with recurrent or refractory leukemias or solid tumors (Study INCB 84344-102). The final dataset for PopPK analysis included 2745 concentrations from 315 study participants, of which 232 PK samples were from 55 paediatric study participants. Baseline covariates of adult and paediatric study participants in the combined dataset evaluated in this PopPK analysis are summarized in Table 4**.**

Table 4 Summary of Baseline Covariates in the Population PK Dataset

Covariate	**Less than 6 years (N=8)**	**6 to less than 12 years (N=15)**	**12 to less than 18 years (N=32)**	**Adult (N=260)**	**Overall (N=315)**
Age (year)					
Mean (SD)	3.65 (1.44)	9.13 (1.94)	15.1 (1.69)	49.0 (14.3)	42.5 (19.3)
Median [Min, Max]	3.85 [1.50, 5.00]	9.60 [6.00, 11.9]	14.8 [12.0, 17.7]	49.0 [19.0, 85.0]	44.0 [1.50, 85.0]
Weight (kg)					
Mean (SD)	16.0 (4.03)	30.7 (8.91)	54.7 (13.5)	79.0 (17.2)	72.7 (22.3)
Median [Min, Max]	14.9 [10.9, 21.9]	28.5 [17.5, 48.0]	54.8 [26.3, 80.0]	77.2 [40.7, 152]	73.4 [10.9, 152]

Dose (mg)					
2	0 (0%)	0 (0%)	0 (0%)	3 (1.2%)	3 (0.9%)
4	0 (0%)	0 (0%)	0 (0%)	6 (2.3%)	6 (1.9%)
5	4 (50.0%)	0 (0%)	0 (0%)	0 (0%)	4 (1.3%)
8	0 (0%)	0 (0%)	0 (0%)	7 (2.7%)	7 (2.2%)
15	4 (50.0%)	8 (53.3%)	3 (9.4%)	34 (13.1%)	49 (15.5%)
20	0 (0%)	0 (0%)	2 (6.3%)	0 (0%)	2 (0.6%)
30	0 (0%)	5 (33.3%)	12 (37.5%)	13 (5.0%)	30 (9.5%)
45	0 (0%)	2 (13.3%)	15 (46.9%)	177 (68.1%)	195 (61.7%)
60	0 (0%)	0 (0%)	0 (0%)	19 (7.3%)	19 (6.0%)
135	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	1 (0.3%)
Formulation					
Tablet	0 (0%)	0 (0%)	32 (100%)	203 (78.1%)	236 (74.7%)
Capsule	1 (12.5%)	14 (93.3%)	0 (0%)	57 (21.9%)	72 (22.8%)
Mini tablet	7 (87.5%)	1 (6.7%)	0 (0%)	0 (0%)	8 (2.5%)
Sex					
Female	5 (62.5%)	4 (26.7%)	19 (59.4%)	179 (68.8%)	208 (65.8%)
Male	3 (37.5%)	11 (73.3%)	13 (40.6%)	81 (31.2%)	108 (34.2%)

Abbreviations: ALT = alanine transaminase; BMI = body mass index; BSA = body surface area; N = number of participants. Note: - = not available.

Figure 1 presents individual ponatinib plasma concentration–time profiles for adult and paediatric study participants.

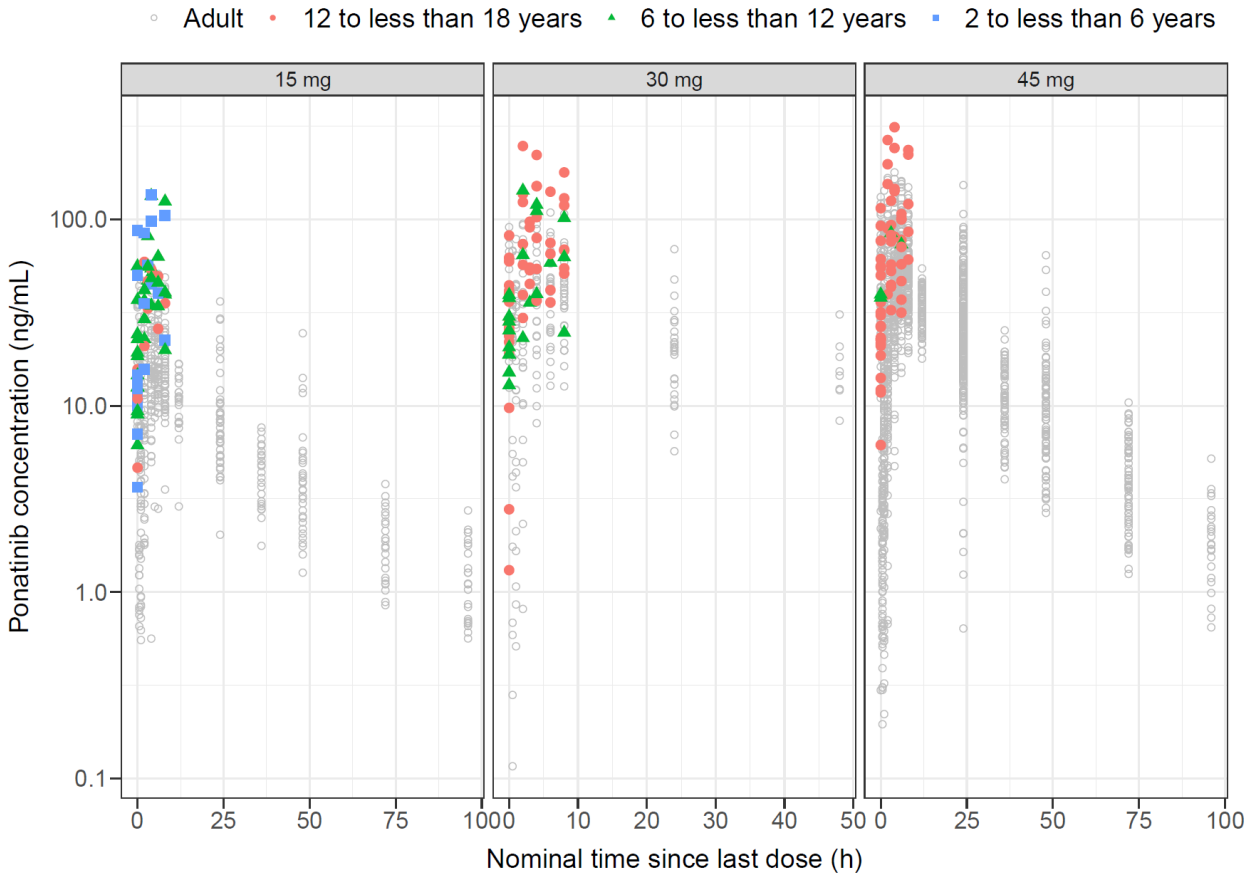


Figure 1 Ponatinib Plasma Concentration versus Time After Dose in Adults and Paediatric Cohorts.

The previously developed PopPK model in adults was updated with the addition of paediatric PK data. Clearance and volume terms were allometrically scaled based on body weight raised to the power of 0.75 for CL/F and Q/F and 1 for Vc/F and Vp/F. Similar to the adult PopPK model, a two-compartment disposition structure with linear elimination from the central compartment and dual first-order absorption processes was used (Table 5). Apart from body weight, no new covariate effects were identified compart to the adult PopPK model.

Table 5. Comparison of Original Parameter Estimates (Adults Only) and Final Population PK Parameter Estimates for Ponatinib in Adult Healthy Volunteers, Adult Study Participants with Hematologic Malignancies and Paediatric Study Participants with Hematologic and Solid Malignancies

		Run219#			**Original model***		
Parameter	**Unit**	**Estimate (CV%)**	**RSE (%)**	**Shrinkage (%)**	**Estimate (CV%)**	**RSE (%)**	**Shrinkage (%)**
CL/F	L/h	33.1	3.16		34.3	3.41	
Vc/F (V3/F)	L	754	3.89		839	4.22	
Q/F	1/h	16.1	8.07		17.2	9.19	
Vp/F (V4/F)	L	316	3.16		347	3.08	
Tlag2	h	3.93 Fixed	-		3.93	0.17	
Ka1/F	1/h	1.32	3.88		1.3	4.08	

Ka2/F	1/h	4.41 Fixed	-		4.41 Fixed		
F2-HV	%	46.6 Fixed	-		46.6	31.8	
F2-Cancer		0 Fixed	-		0 Fixed		
Age effect on Vc/F (adults only)		0.646	16.6		0.645	16.4	
WT effect on CL/F and Q/F		0.75 (fixed)			-	-	
WT effect on Vc/F and Vp/F		1 (fixed)			-	-	
WT effect on Vc/F		-			0.5038	27.8	
IIV							
Omega CL/F		0.247 (52.9%)	10.2	6.42	0.231 (48%)	10.9	6.4
Covariance CL/F-Vc/F		0.139	15.9		0.130	18.8	
Omega Vc/F		0.197 (46.7%)	12	21.6	0.179 (42.3%)	12.9	20
Omega Ka		0.213 (48.7%)	11.4	23.4	0.219 (46.8%)	12.1	19
Residual Error (%)							
HV		14.7	2.66		14.9	2.81	
Cancer		38.4	0.57		38.6	0.62	

Abbreviations: Cancer = adult and paediatric study participants with hematologic malignancies and paediatric study participants with solid tumors, CL/F = apparent clearance, CV = coefficient of variation, F2-HV = bioavailability of route 2 in healthy volunteers, F2-Cancer = bioavailability of route 2 in patients with cancer, HV= healthy volunteers, Ka = absorption rate constant, IIV = interindividual variability, PK = pharmacokinetics, Q/F = apparent intercompartmental clearance, RSE = relative standard error, Vc/F, V3/F = apparent volume of the central compartment, Vp/F, V4/F = apparent volume of the peripheral compartment. Notes: *Original model was developed in adult healthy volunteers and adult study participants with hematologic malignancies (see PopPK report CPP-25.39.1). #Run219 was developed in adult healthy volunteers, adult study participants with hematologic malignancies and paediatric study participants with hematologic and solid malignancies; RSE calculated as standard error/estimate x 100; CV% = $\sqrt{}ew2 - 1 \times 100$.

A pcVPC demonstrated that the final model adequately captured the central tendency and variability of the observed ponatinib concentrations in paediatric patients (Figure 2). Furthermore, the model performed well in the paediatric subpopulation stratified by body weight (Figure 3).

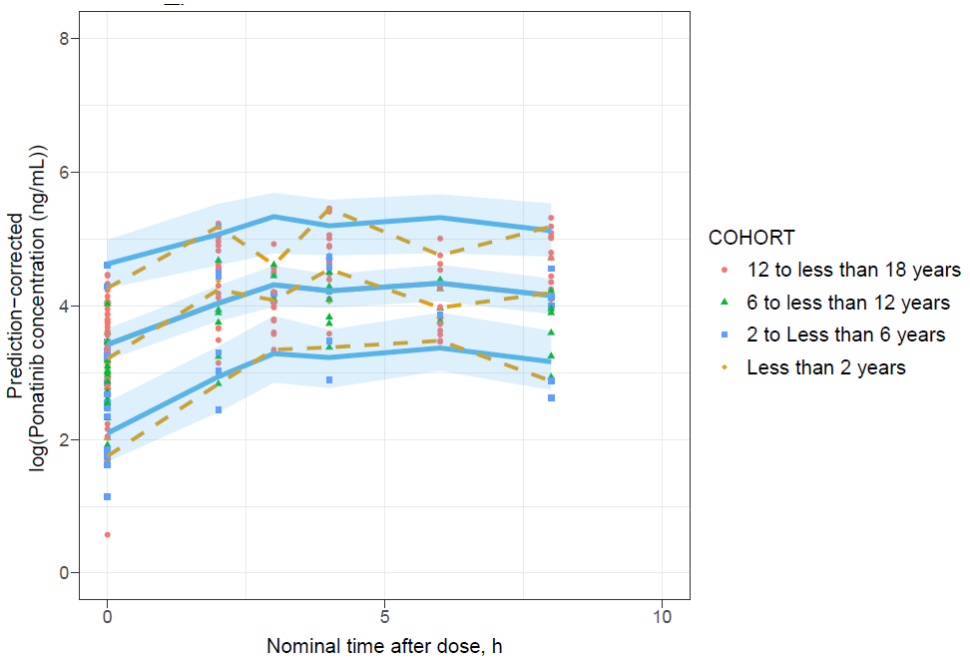


Figure 2 pcVPC for the Final PopPK Model for Paediatric Subpopulation versus Time After Dose. Abbreviations: pcVPC = prediction-corrected visual predictive check, PopPK = population pharmacokinetics. Notes: Colored dots are individual prediction-corrected values. Orange dashed lines represent the 5th, 50th (median) and 95th percentiles of the observed ponatinib concentrations over time. Solid blue lines represent the 5th, 50th (median) and 95th percentiles of the predictions from 1000 simulations. Blue bands present the 90% confidence interval around each simulated percentile

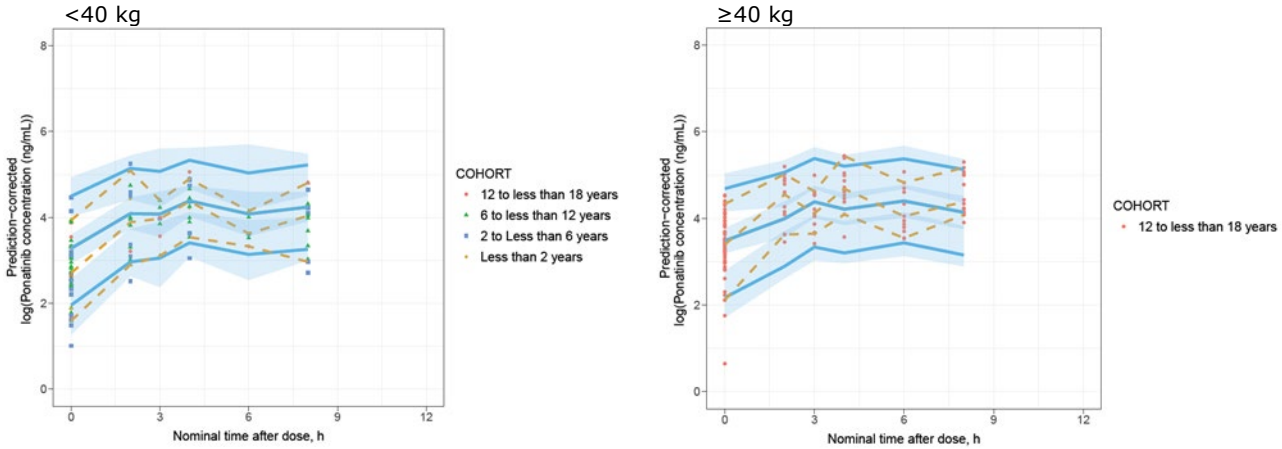


Figure 3 pcVPC for the Final PopPK Model for Paediatric Subpopulation versus Time After Dose by Weight Groups. Abbreviations: pcVPC = prediction-corrected visual predictive check, PopPK = population pharmacokinetics. Notes: Colored dots are individual prediction-corrected values. Orange dashed lines represent the 5th, 50th (median) and 95th percentiles of the observed ponatinib concentrations over time. Solid blue lines represent the 5th, 50th (median) and 95th percentiles of the predictions from 1000 simulations. Blue bands present the 90% confidence interval around each simulated percentile

The MAH proposed a paediatric posology consisting of three weight bands (15 to less than 30 kg, 30 to less than 45 kg and 45 kg or greater). This was supported by a simulation-based exposure comparison compared to adults.

Simulated paediatric exposures were compared against a target exposure range based on the expected exposure in adult patients. The adult target exposure range was based on simulations of the steady-state exposure following 45 mg QD (starting dose) from the adult PopPK model. The adult body weight

distribution for these simulations were generated by sampling observed body weights in adult CP-CML patients from Europe that were enrolled in the OPTIC 5-year study (AP24534-14-203). Corresponding target exposure ranges were derived for the reduced dose of 15 mg QD.

The paediatric simulations were based on the final paediatric PopPK model (with fixed allometric exponents). For these simulations, body weight was sampled from CDC growth charts. 500 patients were simulated per kg body weight (250 females and 250 males). The 90% prediction interval of the paediatric simulations were compared with the adult target exposures in Figure 4 (15-45 kg) and Figure 5 (>45 kg).

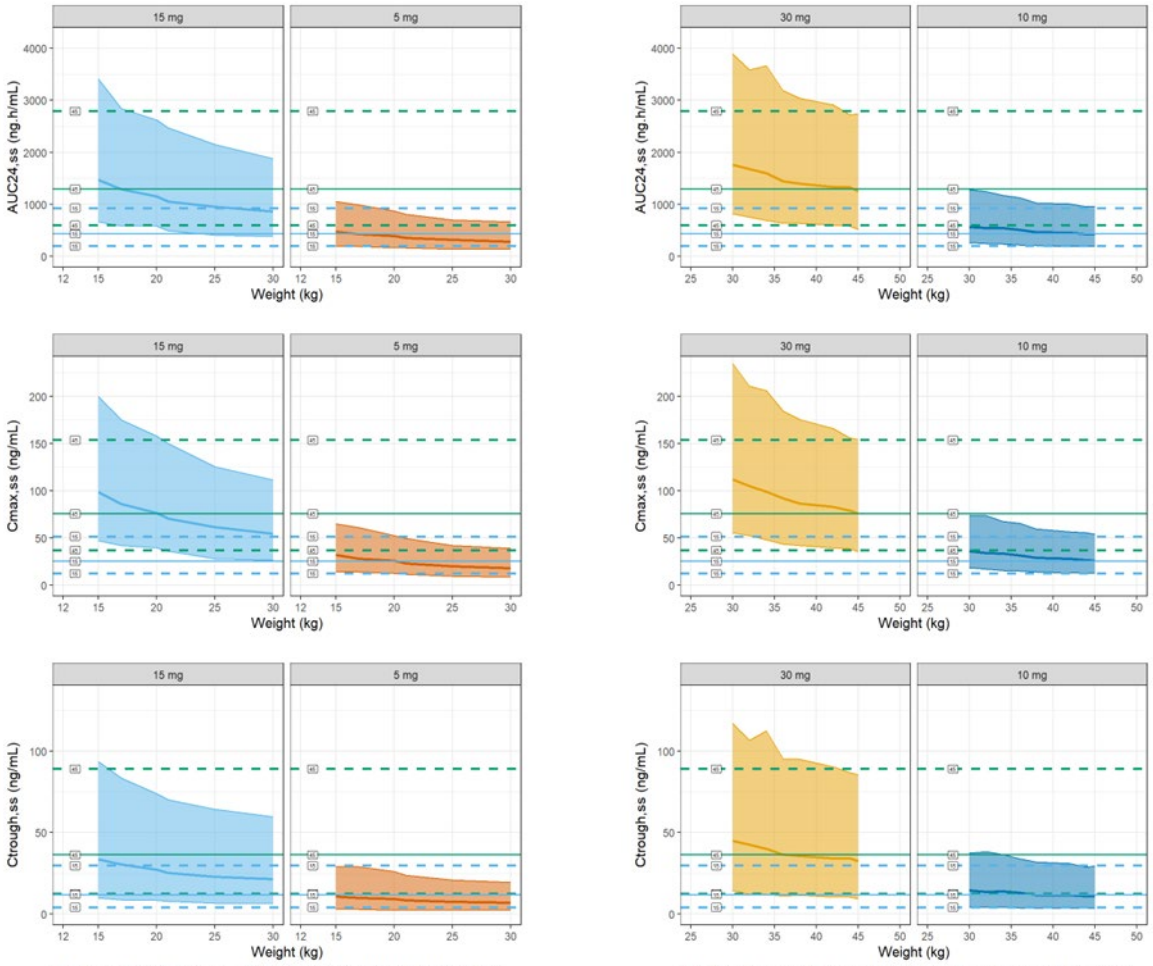


Figure 4 Simulated exposures in paediatric patients 15-45 kg according to proposed posology compared to exposures in adult patients

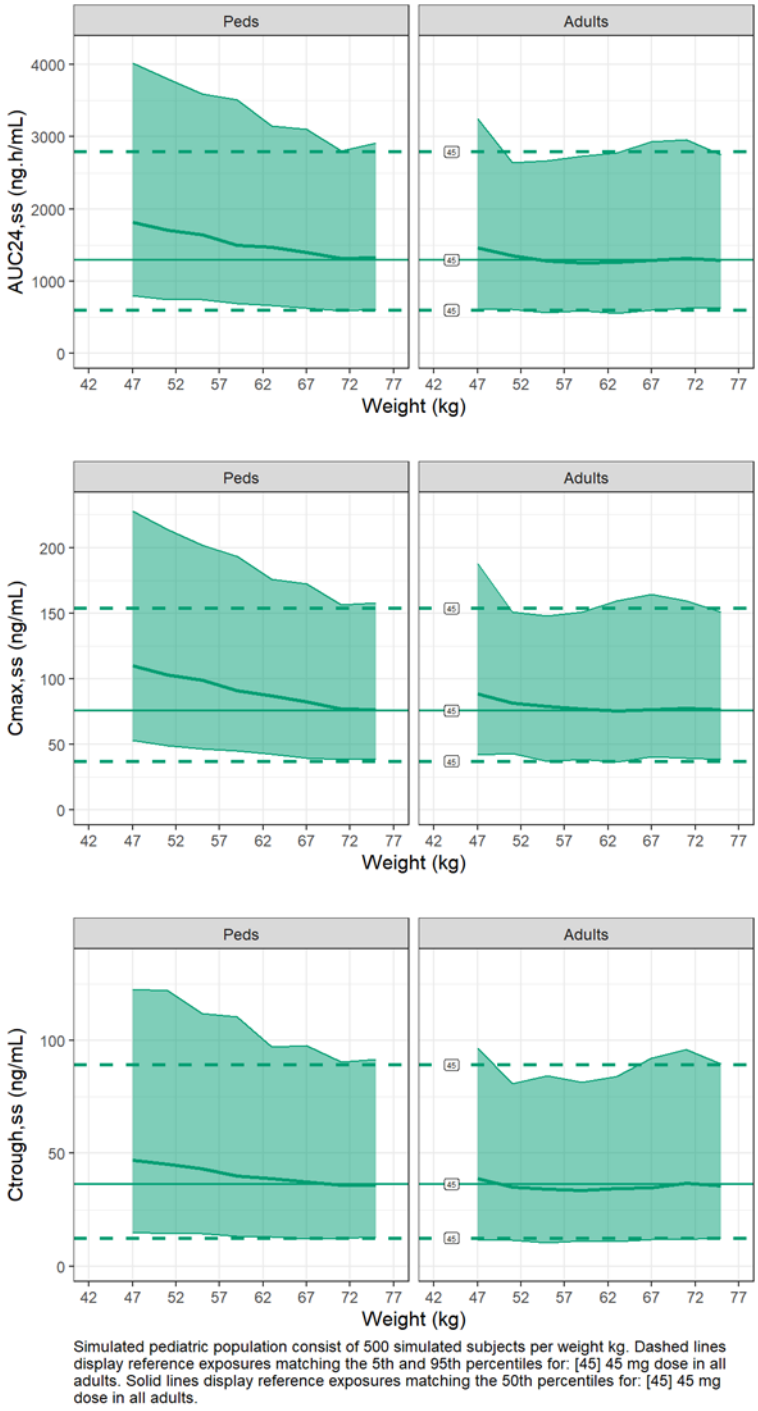


Figure 5 Simulated exposures in paediatric and adult patients > 45 to 75 kg for 45 mg QD.

A sensitivity analysis was conducted in which the fixed body weight exponents in the final PopPK model were estimated.

5.2.2.3. Absorption

For the pharmacokinetic results in the target paediatric population see section 5.2.2.2.1 Population Pharmacokinetics.

Absolute oral bioavailability of ponatinib in humans has not been determined. Ponatinib HCl is considered a "low solubility" compound due to its insolubility in aqueous solution above pH 2. Combined with high permeability assessed using the Caco-2 cell transport, ponatinib is categorised as a BCS Class II compound.

5.2.2.4. Bioequivalence

Capsules of ponatinib were developed for administration in paediatric patients. The first capsule formulation developed was the "enabling" capsule, which contained a 5 mg powder formulation of ponatinib. A bioavailability (BA) study, **INCB84344-101**, was subsequently performed to compare the "enabling" formulation with the commercial adult tablet of 15 mg. Additionally, this study examined the bioavailability of the capsule when administered intact versus when opened and sprinkled in yoghurt or applesauce.

For marketing, a second capsule formulation was developed, designed to facilitate more accurate dosing. This formulation, denominated MiniTab capsules, contains 0.5 mg x 10 mini-tablets of ponatinib with a similar composition as the adult tablet. Like the first capsule, the MiniTab capsule underwent comparison with the adult tablet of 15 mg, and tests of the capsule intact versus opened and sprinkled in yoghurt and applesauce, as part of study **INCB84344-103.**

Enabling capsule Study INCB84344-101

The study, INCB 84344-101, was a Phase 1, open-label, randomized, 2-cohort crossover trial conducted to evaluate the relative bioavailability of ponatinib 5 mg "enabling" capsules administered orally in healthy subjects.

In total, 40 participants were enrolled in this study (16 participants in Cohort 1 and 24 participants Cohort 2). Cohort 1 was a 2-period crossover and Cohort 2 was a 3-period crossover. In total 38 participants completed the study. One participant in Cohort 2 was withdrawn from the study due to a protocol deviation (nicotine product use) and another participant in Cohort 2 was withdrawn due to an AE of chest pain.

The results showed that the relative bioavailability of ponatinib 5 mg capsules was comparable to that of the 15 mg tablet. The geometric mean ratio (GMR) of the area under the plasma concentration-time curve (AUC0-∞) for the 3 × 5 mg capsules versus the 15 mg tablet was 99.2% (90% CI: 94.6%-104%). The GMR for Cmax and AUC0-t was 102% (90% CI: 94.8%-111%) and 98.7% (90% CI: 94.1-104%) respectively. The mean Tmax was 4.98 h for the 15 mg tablet and 4 h for the 3 x 5 mg capsules.

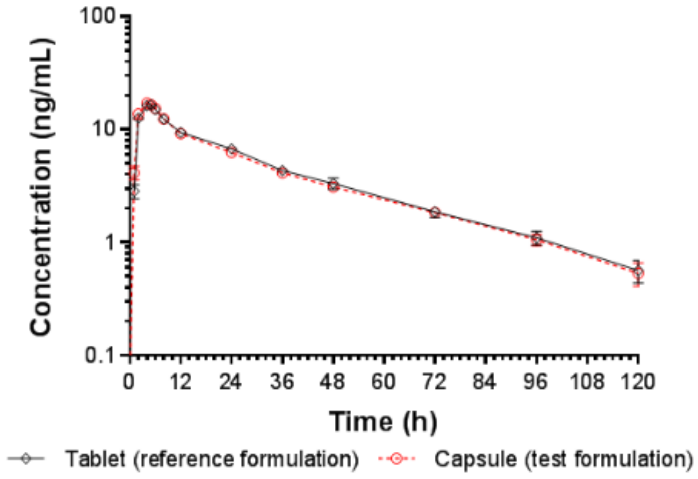


Figure 6 Plasma concentrations of ponatinib (mean ± SE) in healthy participants following administration of ponatinib 15 mg tablet and 3 × 5 mg capsules.

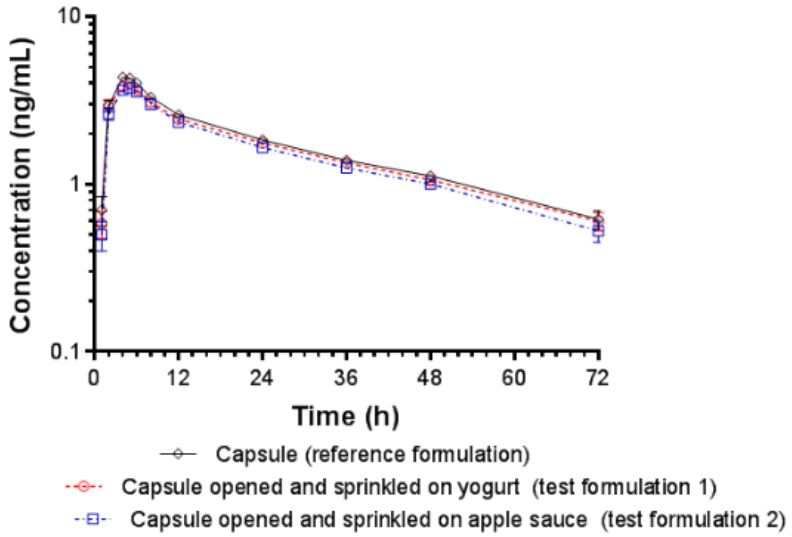


Figure 7 Plasma concentrations of ponatinib (mean ± SE) in healthy participants following administration of ponatinib 5 mg capsule intact and capsule opened and sprinkled on yogurt or applesauce

The GMR of AUC0-∞ for the 5 mg capsule intact versus the 5 mg capsule opened and sprinkled on yogurt was 93.5% (90% CI: 87.6%-99.8%), and the GMR of AUC0-∞ for the 5 mg capsule intact versus the 5 mg capsule opened and sprinkled on applesauce was 87.3% (90% CI: 81.8%-93.2%). The $AUC_{0-\infty}$ was within the 80% to 125% limits, but the Cmax and AUC0-t were outside limits when the "enabling" capsules were opened and sprinkled on applesauce relative to intact "enabling" capsules administered in the fasted state. The 90% CI of C_{max} and AUC_{0-t} were 77.3%-92.3% and 76.5-90.6%, respectively, indicating a slightly lower exposure when administered opened and sprinkled on applesauce. (N.B. comparison was done between opened vs intact, i.e. test/reference, while Table 6 indicates that the comparisons were reference/test).

Table 6. Comparison of ponatinib pharmacokinetic parameters following administration of ponatinib 5 mg capsule intact and 5 mg capsule opened and sprinkled on yogurt or applesauce

	C_{max}	t_{max}	AUC_{0-t}	$AUC_{0-\infty}$	$t_{½}$
P-values from a crossover ANOVA of log-transformed data					
Formulation	0.0071	0.439	0.0031	0.0046	0.104
Sequence	0.531	–	0.712	0.837	0.940
Period	0.721	–	0.0018	0.0007	0.04
GM ratios and 90% CIs (reference = ponatinib 15 mg tablet)					
Capsule intact vs capsule opened and sprinkled on yogurt (Treatment C vs D)	87.6% 80.1%-95.8%	–	89.6% 82.3%-97.6%	93.5% 87.6%-99.8%	–
Capsule intact vs capsule opened and sprinkled on applesauce (Treatment C vs E)	84.5% 77.3%-92.3%	–	83.2% 76.5%-90.6%	87.3% 81.8%-93.2%	–

Commercial capsule Study INCB84344-103

The study INCB 84344-103 was a randomized, open-label, 2-cohort, crossover relative bioavailability study in healthy participants. The primary objectives were to compare the relative bioavailability of ponatinib 5 mg × 3 MiniTab capsules with a commercial ponatinib 15 mg tablet and to compare the relative bioavailability of ponatinib 5 mg × 3 MiniTab capsule contents sprinkled on yogurt or applesauce with intact MiniTab capsules.

Cohort 1 was a 2-period crossover, and Cohort 2 was a 3-period crossover. Thirty-seven participants completed the study and 3 participants chose to withdraw from the study. One participant withdrew from Cohort 1 on Day 6 after receiving 1 dose of ponatinib (15 mg tablet). Two participants withdrew

from Cohort 2, of whom 1 participant withdrew on Day 49 after receiving 2 doses of ponatinib and 1 participant withdrew on Day 52 after receiving all 3 doses of ponatinib.

The results showed that the GMR of ponatinib 5 mg × 3 MiniTab capsules was 103% compared to the commercial ponatinib 15 mg tablet, with a 90% CI of 97.8% to 109%. The GMR for Cmax and AUC0-t was 104% (90% CI: 97.2%-110%) and 104% (90% CI: 98.3-110%) respectively. The mean Tmax was 6 h for both the 15 mg tablet and for the 3 x 5 mg capsules.

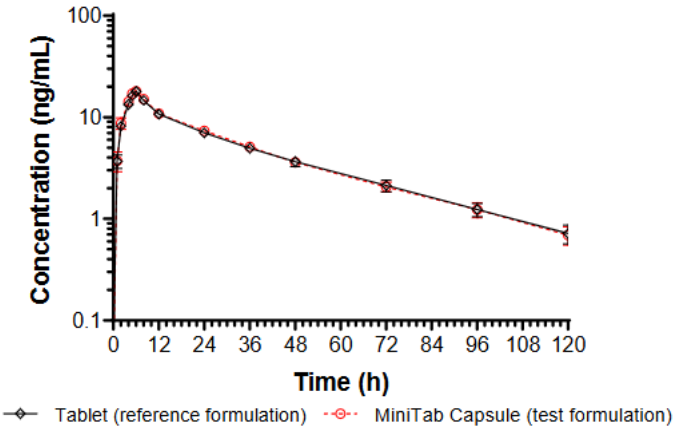


Figure 8 Plasma concentrations of ponatinib (mean ± SE) in healthy participants following administration of ponatinib 15 mg tablet and 3 × 5 mg Minitab capsules

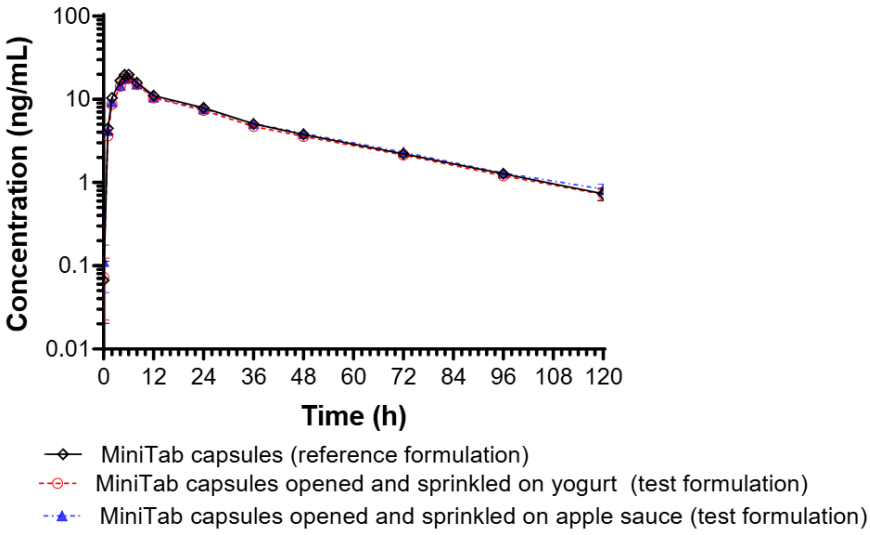


Figure 9 Plasma concentrations of ponatinib (mean ± standard error) in healthy participants following administration of ponatinib 5 mg MiniTab capsules intact and capsules opened and sprinkled on yogurt or applesauce

The GMR of AUC0-∞ for the MiniTab capsule contents intact versus the MiniTab capsule contents sprinkled on yogurt was 93.0% (90% CI: 88.8%-97.4%), and the GMR of AUC0-∞ for the MiniTab capsule contents intact versus the MiniTab capsule contents sprinkled on applesauce was 95.9% (90% CI: 91.5%-101%). The GMR of AUC0-t was 93.4% (90% CI: 89.0%-98.1%) for yogurt and 96.2% (90% CI: 91.5%-101%) for applesauce, while the GMR of Cmax was 89.6% (90% CI: 84.3%-95.1%) for yogurt and 89.5% (90% CI: 84.2%-95.1%) for applesauce, indicating that the bioavailability of ponatinib was comparable under all of these different administration conditions.

Table 7 Comparison of ponatinib pharmacokinetics following administration of ponatinib 3 × 5 mg MiniTab capsules intact and 3 × 5 mg MiniTab capsules opened and sprinkled on yogurt or applesauce

	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (h·ng/mL)	$AUC_{0-\infty}$ (h·ng/mL)	$t_{½}$ (h)
Geometric mean ratios and 90% CIs (reference = ponatinib intact MiniTab capsules)					
MiniTab capsules intact vs MiniTab capsules opened and sprinkled on yogurt (Treatment C vs D)	89.6% 84.3%-95.1%	–	93.4% 89.0%-98.1%	93.0% 88.8%-97.4%	–
MiniTab capsules intact vs MiniTab capsules opened and sprinkled on applesauce (Treatment C vs E)	89.5% 84.2%-95.1%	–	96.2% 91.5%-101%	95.9% 91.5%-101%	–
P-values from a crossover ANOVA of log-transformed data					
Formulation	0.0039	0.144	0.0718	0.0398	0.827
Sequence	0.794	–	0.766	0.728	0.389
Period	0.600	–	0.0021	0.0017	0.196

ANOVA = analysis of variance; $AUC_{0-\infty}$ = area under the single-dose plasma concentration-time curve extrapolated to time of infinity; AUC_{0-t} = area under the plasma concentration-time curve from time = 0 to the last measurable concentration at time = t; CI = confidence interval; C_{max} = maximum observed plasma concentration; $t_{½}$ = apparent terminal-phase disposition half-life; t_{max} = time to maximum concentration.
Source: DMB-20.20.1 Table 7.

5.2.2.5. Distribution

For the pharmacokinetic results in the target paediatric population see section 5.2.2.2.1 Population Pharmacokinetics.

5.2.2.6. Metabolism

Not applicable. Maturation responsible for elimination of small molecule drugs can generally be assumed to be on-going below 2 years of age. The proposed indication is limited to patients aged 6 years and older where no on-going maturation is expected.

5.2.2.7. Elimination

For the pharmacokinetic results in the target paediatric population see section 5.2.2.2.1 Population Pharmacokinetics.

5.2.2.8. Dose proportionality and time dependency

Dose proportionality was assessed in the original procedure for Iclusig (EMEA/H/C/2695) based on study AP245334-07-101. PK was concluded to be roughly dose proportional in the therapeutic range in adults for ponatinib (15-45 mg). Re-evaluating these data, in adults, ponatinib can be considered roughly dose-proportional between 8-45 mg.

Table 8 Dose-normalised AUC_{0-t} and Cmax values based on data from study AP245334-07-01

Dose (mg)	AUC (gMean)	Cmax (gMean)	AUC_{0-t} /Dose	Cmax/Dose
2	47.7	2,5	23,8	1,2
4	97.9	5,7	24,5	1,4
8	290.9	14,6	**36,4**	**1,8**
15	451.8	25,8	**30,1**	**1,7**
30	1080	64,6	**36,0**	**2,2**
45	1296	77,4	**28,8**	**1,7**
60	1521	97,5	25,4	1,6

Bold = suggested dose range

The lowest proposed daily dose for paediatric patients is 5 mg (for patients 15-30 kg who require dose adjustment due to toxicity). Exposure matching between paediatric and adult populations have been conducted through popPK analysis. The paediatric popPK analysis were not indicative of any relevant dose non-linearity in PK parameters in paediatric patients.

5.2.2.9. Pharmacokinetics in the target population

For the pharmacokinetic results in the target paediatric population see section 5.2.2.2.1 Population Pharmacokinetics.

The PK in the target population is derived from ongoing study INCB 84344-102 in paediatric participants (≥ 1 to < 18 years) with advanced leukaemia's, lymphomas, or solid tumours, in addition to an expansion cohort focused on paediatric participants with CP-CML. The overall number of paediatric patients was small, especially with the proposed indication CP-CML, so PK samples were limited, and variability was high. The PK sampling design in the paediatric study was based on a sparse sampling scheme which means that non-compartmental analysis approaches are not relevant for analysing these data. Thus, popPK modelling was used to describe the PK in the target population. In addition, the studied doses differ from the proposed posology in the SmPC for the lower-weight patients (<30 kg).

Study Ponatinib-1501 was prematurely terminated, and PK data were limited. It is not used to describe the PK through popPK analysis for the target population.

5.2.2.10. Special populations

No new data has been submitted.

5.2.2.11. Pharmacokinetic interaction studies

No new data has been submitted.

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Ponatinib is an orally available TKI, with BCR-ABL1 as a primary target. Ponatinib inhibits both native BCR-ABL1 and its mutant forms, including the T315I gatekeeper mutation that confers resistance to other approved TKIs that target BCR-ABL1 (ie, imatinib, dasatinib, nilotinib, and bosutinib). Through direct inhibition of native BCR-ABL1 and its variants, ponatinib inhibits aberrant downstream signaling by reducing phosphorylated crk-like protein, thereby promoting apoptosis and cell death in BCR-ABL1–positive cells (O'Hare et al 2009).

5.2.3.2. Primary and secondary pharmacology

Not applicable.

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

Not applicable.

5.2.3.4. Genetic differences in PD response

Not applicable.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Analyses were performed from PK and safety data obtained in Study INCB 84344-102 to assess the relationship between ponatinib steady-state exposure (AUC0-24 on Cycle 1 Day 15) in participants who had Grade 3 or higher TEAEs relative to those who did not.

As shown in Figure 10, these analyses indicate no difference in exposure for participants with a Grade 3 or higher TEAE compared to exposures in participants who did not have these type of TEAEs.

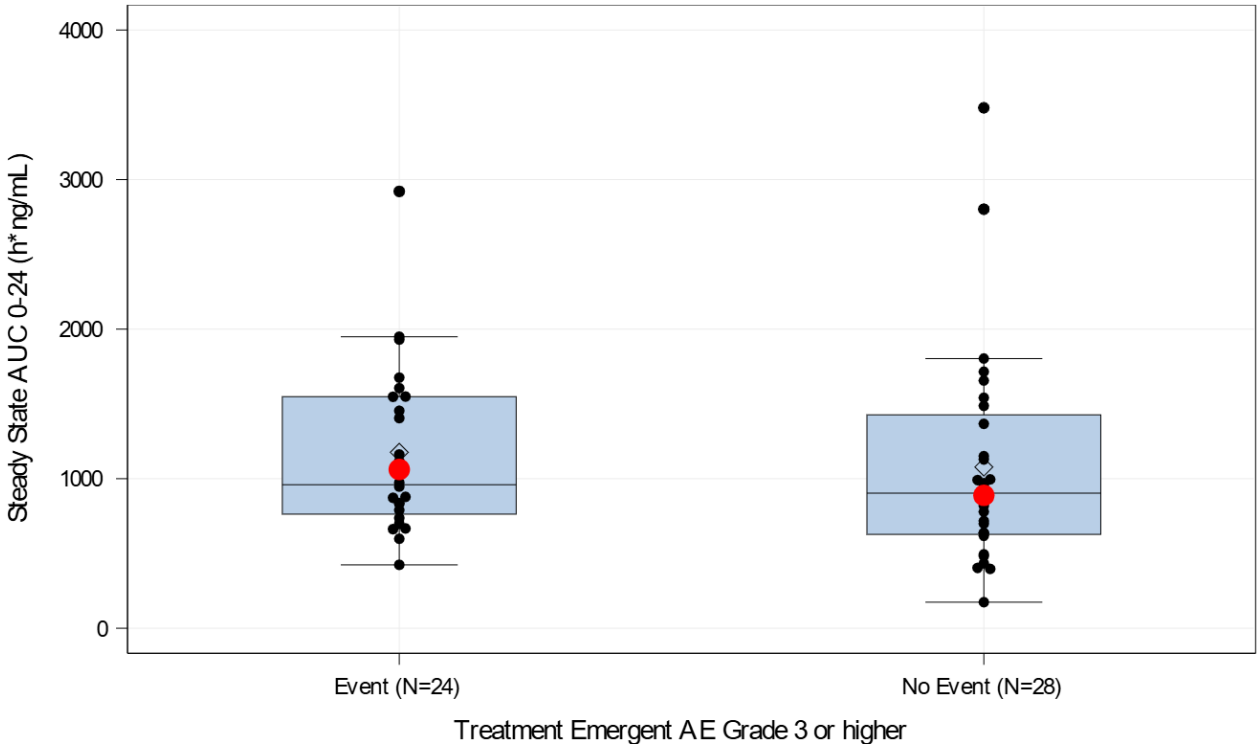


Figure 10 Boxplot of Ponatinib AUC0-24 h for Participants Experiencing Versus Not Experiencing Grade 3 or Higher TEAEs. Notes: Each box represents the interquartile range (25th to 75th percentile) of the observed values; the horizontal bar within a box is the median; the diamond symbol inside a box is the arithmetic mean; the red circle is the geometric mean; individual values are shown as black circles. Whiskers below and above each box represent subtraction from 1.5 times the lower quartile or addition of 1.5 times the upper quartile, respectively.

5.2.5. Dose selection and therapeutic window

Ponatinib concentration measures obtained from participants enrolled in the paediatric efficacy and safety Study INCB 84344-102 (as of data cutoff date: 25 JAN 2025) supported development of an adult-paediatric popPK model that enabled simulations of different dose strategies that would achieve ponatinib exposures consistent with those defined in adults that optimize benefit- risk outcomes. The approved starting dose to establish a therapeutic response in adult participants with CP-CML is 45 mg QD. Simulations from the adult-paediatric model (see Section 5.2.2.2.1) have led to the following weight-adjusted starting doses for paediatric participants (≥ 6 to < 18 years) that are predicted to lead to exposures that match exposures in adults taking the 45 mg QD regimen.

▪ 15 mg QD, ≥ 15 to < 30 kg

▪ 30 mg QD, ≥ 30 to < 45 kg

▪ 45 mg QD, ≥ 45 kg

As in adults, the risk of arterial occlusive events is likely to be dose related. Reducing the dose of Iclusig according to Table 8 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 (see SmPC sections 4.4 and 5.1). 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.

Table 9 Recommended dose reduction for paediatric patients after achieving a molecular response

Weight	Starting dose in mg (once daily)	Recommended reduced dose in mg (once daily
≥45 kg	45 mg	15 mg
≥30 and <45 kg	30 mg	10 mg
≥15 and <30 kg	15 mg	5 mg

Dose modifications were also recommended in paediatric patients based on occurrence of certain AEs according to the SmPC section 4.2.

Similar to adults, a reduced starting dose is recommended in paediatric patients on concomitant CYP3A4 inhibitors; 20 mg QD is recommded in paediatric patients between 30-45 kg and 10 mg QD is recommended in paediatric patients 15-30 kg.

Regarding therapeutic window, the proposed dose was based on a PK-bridge with exposure comparison between paediatric patients and adults. The proposed doses were chosen to achieve ponatinib exposures consistent with those defined in adults. Thus, the proposed dose was not based on a conventional therapeutic window based on knowledge of exposure-response relationships in efficacy and safety endpoints.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Bioanalytical Methods

The assay methods are considered adequate to quantify drug concentrations of ponatinib.

In-study bioanalytical reports were included for Studies INCB 84344-101, Study INCB 84344-102, Study Ponatinib-1501 and Study INCB 84344-103.

For studies with a submitted bioanalysis report, all clinical samples were analysed within the established stability period of the analyte. Overall the determination of ponatinib in human plasma showed adequate performance. ISR assessments were conducted and met the acceptance criteria for all studies.

Bioequivalence

Two relative bioavailability studies were submitted, study INCB84344-101 and study INCB84344-103. Study INCB84344-101 compared the "enabling" powder filled capsule used in clinical studies with the adult commercial tablet of 15 mg. Study INCB84344-103 compared the new paediatric formulation Minitab capsules (0.5 mg x 10 mini-tablets of ponatinib with a similar composition as the adult tablet), with the commercial adult tablet of 15 mg. Both capsules were also compared administered opened and sprinkled in yoghurt or applesauce versus intact.

In study INCB 84344-102, the enabling capsule was administered to the majority of relevant patients for this application (14 out of 15 patients in the age group 6-12 years, as stated in the popPK report (CPP-25.39.1). Since the commercial formulation is the MiniTab capsule, it is essential for the extrapolation that the different formulations of the capsule can be considered similar in bioavailability.

Both capsules (3 x 5 mg) were studied in comparison with the commercial adult tablet formulation of 15 mg. However, the capsules were compared to the adult formulation in two separate studies, thus there was no direct PK bridge between the capsules, while direct bridges are established to the adult tablet formulation. This can be considered acceptable, since both studies showed that all measured PK parameters (C_{max} and AUC_{0-t} and $AUC_{0-\infty}$) were within standard bioequivalence (BE) acceptance limits of 80-125%, including 100% with similar point estimates, and that the 90% CIs for both formulations are largely overlapping. Thus, the two formulations of capsules ("enabling" and "MiniTabs") are considered similar to each other in bioavailability. Additionally, as this is a line-extension application, strict BE criteria do not apply.

Both capsules were also administered intact or opened and sprinkled on either yoghurt or apple sauce. For the enabling capsule opened and sprinkled on applesauce vs the intact capsule, the $AUC_{0-\infty}$ was within the 80% to 125% limits, but the 90% CI of C_{max} and AUC_{0-t} were slightly outside limits (C_{max} 90% CI: 77.3%-92.3% and AUC0-t: 76.5-90.6%) indicating a lower exposure when administered opened and sprinkled on apple sauce. According to the Quality assessment report, there was no stability issue of the formulation in apple sauce. It is not entirely clear from the CSR of study INCB 84344-102, how many children between 6-12 years that were given the enabling capsule sprinkled on apple sauce. If a significant number, the popPK analysis may theoretically underestimate exposures (Cmax is of main concern for safety) compared with the commercial formulation. Documentation provided indicates that 7/31 powdered capsule doses were given opened, and one of these are notated to be with yoghurt, but none with apple sauce. Although there is still an uncertainty as to how these 6 opened doses were administered, the majority of doses were capsules swallowed whole. Therefore, the issue is not considered to have a relevant effect on the popPK analysis nor clinical significance and is thus not further pursued.

Moreover, since the commercial formulation, MiniTabs, displayed $C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$ within the standard BE limits, compared with 15 mg tablet or when intact or opened and sprinkled on applesauce or yogurt, it can be concluded that intact MiniTab capsules, and MiniTab capsules opened and sprinkled on yogurt or apple sauce have similar bioavailability, and thus either administration method could be used.

Influence of food

No specific study to investigate the effects on food for the new formulation has been conducted. This is acceptable, given that the commercial tablet formulation has not displayed a relevant food effect. The Minitab is thus not expected to differ in terms of food effect on PK.

Dose-proportionality

It was previously concluded that the PK was roughly dose proportional in the therapeutic range for ponatinib (15-45 mg). Study AP245334-07-101 included dose levels of 2 mg, 4 mg, 8 mg, 15 mg,

30 mg, 45 mg and 60 mg, given to achieve steady state. According to the assessment at original MAA, there was limited assay sensitivity and poor definition of the elimination phase for the lower doses. There were also some indications of non-linearity of AUC_{0-t} with dose from the single dose data at these lower dose levels (4 mg, 2 mg).

The ratio of geometric mean (gMean) AUC_{0-t} /Dose and Cmax/Dose was slightly lower for AUC and Cmax at 2 mg and 4 mg, but for 8 mg, it was within the range of the previously established dose-proportionality (see table 13). The number of subjects in the 8 mg dose group was 6, and the %CV was relatively low of 21.8 and 24.4% for Cmax and AUC, respectively (study AP245334-07-101). Based on these data in adults, ponatinib can be considered roughly dose-proportional between 8-45 mg.

Table 10 Dose-normalised AUC_{0-t} and Cmax values based on data from study AP245334-07-01

Dose (mg)	AUC (gMean)	Cmax (gMean)	AUC_{0-t} /Dose	Cmax/Dose
2	47.7	2,5	23,8	1,2
4	97.9	5,7	24,5	1,4
8	290.9	14,6	**36,4**	**1,8**
15	451.8	25,8	**30,1**	**1,7**
30	1080	64,6	**36,0**	**2,2**
45	1296	77,4	**28,8**	**1,7**
60	1521	97,5	25,4	1,6

Bold = new suggested dose range

The paediatric popPK analysis were not indicative of any relevant dose non-linearity in PK parameters in paediatric patients. The paediatric PopPK model was a pooled paediatric+adult analysis where the model gave acceptable description of both paediatric and adult data. The final paediatric PopPK model included body weight as a covariate on clearance and volume terms using fixed allometric exponents. Despite that no formal evaluation was conducted in the paediatric dataset, this suggests that there are no clinically relevant differences in dose non-linearity and relative bioavailability between children and adults.

Pharmacokinetics in the target population

The PK in the target population is derived from ongoing study INCB 84344-102 in paediatric participants (≥ 1 to < 18 years) with advanced leukaemia's, lymphomas, or solid tumours, in addition to an expansion cohort focused on paediatric participants with CP-CML. The overall number of paediatric patients was small, especially with the proposed indication CP-CML, so that PK samples were limited, and variability was high. The PK sampling design in the paediatric study was based on a sparse sampling scheme which means that non-compartmental analysis approaches are not relevant for analysing these data. Thus, popPK modelling was used to describe the PK in the target population.

The MAH proposed an optimized dose administration strategy for paediatric participants (≥ 6 to < 18 years) with CP-CML based on the PK data observed in Study INCB 84344-102 and the popPK model. The MAH performed simulations to inform the selection of optimal doses included in SmPC 4.2. The paediatric PopPK model is thus considered to have high impact for the benefit-risk assessment. The benefit-risk in paediatric patients ≥6 years is extrapolable from the adult population via PK bridging and extrapolation of efficacy/safety from adults by means of exposure matching which is in line with the EMA guideline recommendations.

The final PopPK model and simulations is considered a reasonable strategy for supporting the proposed paediatric posology in patients ≥6 years.

The amount of data in paediatric patients is sufficient to support development of a paediatric PopPK model. The analysis was a pooled adult+paediatric PopPK model where the amount of paediatric PK data were rather limited compared to the adult data (2745 concentrations from 315 study participants in the PopPK dataset in total).

The distribution of baseline covariates were reasonable. The most critical covariates are age and body weight. Regarding age, there were 8 patients younger than six years which is sufficient to support an indication of ≥6 years. Regarding body weight, the lightest patient weighed 11 kg. 15 kg is the lowest body weight included in SmPC 4.2. A 6 year-old patient will likely not have body weight below 15 kg (based on CDC growth curves).

Formulation (capsule formulation, capsule with mini-tablets, tablet formulation) was not a covariate in the model which is reasonable since the studied paediatric formulations (capsule formulation, capsule with mini-tablets) were bioequivalent to the adult formulation (tablet formulation).

The MAH considered a maturation function on clearance during the PopPK model development. However, no maturation function was included in the final model because it was not supported by the data. This seems reasonable given that there were very few patients below 2 years of age were included in the data. The proposed indication is limited to patients aged 6 years and older where no on-going maturation is expected. Of note, age was included as a covariate in the final model but was only affecting adult patients which is acceptable.

The final model gave acceptable description of the observed paediatric data based on the VPCs stratified on body weight which confirms that the model is fit-for-purpose.

The final model was used to perform PopPK-based simulations to support the proposed posology, including starting doses and reduced doses. The simulations were formatted with PK exposure on the y-axis vs body weight as a continuous variable on the x-axis. The paediatric exposures were included as the 90% prediction interval, which is considered reasonable. The MAH included paediatric simulations including the exposure metrics AUC, Cmax and Ctrough which is acceptable. The paediatric body weights were simulated from the CDC growth chart.

The paediatric simulations were compared with an adult target reference range. The proposed target exposure range is acceptable. Adult target exposure ranges were derived for the recommended adult dose of 45 mg QD which was used for the exposure matching for the paediatric starting dose. In addition, an adult target exposure range was also derived for a 15 mg QD dose which was used for the exposure matching for the reduced paediatric dose. The adult target exposure range was based on an adult body weight distribution sampled from observed body weights from adult CP-CML patients from Europe that were enrolled in the OPTIC 5-year study (AP24534-14-203). The adult target exposure ranges were defined as the 5th to 95th percentiles from the adult simulations.

The proposed paediatric posology is acceptable since the paediatric simulations gave comparable exposure matching compared with the adult target exposure ranges across the three exposure metrics (AUC, Cmax and Ctrough). The dose recommendations are limited to patients with body weights of 15 kg and above which is reasonable; it is unlikely that a patient aged 6 years or older will have body weight below 15 kg. Of note, the MAH provided exposure comparisons for some alternative posologies (data not shown). The degree of exposure matching compared to adults was inferior compared to the proposed doses, which further re-assures the appropriateness of the proposed posologies.

Special populations and PK interaction studies

No new data has been submitted, and this is considered acceptable.

Considering that the adult starting dose is reduced from 45 mg to 30 mg during co-administration with CYP3A4 inhibitors, the MAH proposed corresponding dose adjustments for children ≤ 45 kg co-administered with CYP3A4 inhibitors.

Dose selection

The MAH based the proposed paediatric posology on exposure matching compared to adults rather than a therapeutic window based on knowledge of exposure-response relationships in efficacy and safety endpoints. This is considered a reasonable approach. The PK-bridge and exposure matching is discussed above under "Pharmacokinetics in the target population".

The MAH has adopted a reasonable overall strategy where the relative dose modifications in paediatric patients were comparable to the adult dose modifications.

Exposure-response

The paediatric PK/PD analysis is considered to have rather low impact for the overall benefit-risk assessment.

The paediatric exposure-safety analysis did not indicate any relevant exposure-response relationship. However, no firm conclusions could be drawn due to limitations with the provided PK/PD analysis. Firstly, the dataset was rather limited; It may be difficult to robustly characterise exposure-response relationships for categorical endpoints with ~50 patients. Furthermore, dose modifications based on response was a possibility according to the study protocol which may lead to bias when evaluating exposure-response relationship.

Of note, no exposure-response analysis was performed for efficacy endpoint in paediatric patients which is considered acceptable given that the paediatric exposure-response evaluations are considered to have low impact for the overall benefit-risk assessment.

5.2.6.2. Conclusions

The novel commercial Minitabs formulation is considered to have similar bioavailability to adult tablets and the formulation used in clinical studies. Additionally, using Minitabs by opening and sprinkling them on yoghurt or applesauce as stated in the SmPC section 4.2 is supported by the relative bioavailability studies.

The proposed peadiatric posologies are mainly supported by a PopPK-based PK-bridge with exposure comparison versus adult patients. A paediatric PopPK model is available which is acceptable. The proposed paediatric posology is acceptable.

5.3. Clinical efficacy

The approach to establishing the safety and effectiveness of ponatinib for paediatric use was based primarily on a PK bridging approach.

The primary clinical data supporting efficacy for the paediatric ponatinib indication are from the phase 1/2 study: INCB 84344-102.

5.3.1. Dose response study

The starting dose for Phase 1 Cohort 1 (Dose Level 1) was based upon 80% of systemic exposures achieved at the adult dose of 30 mg. After completion of each age-based cohort in Phase 1, the paediatric recommended Phase 2 dose (RP2D) was determined based on safety and PK data obtained within this component of the study for each cohort independently and extrapolation of data from previous preclinical and clinical studies in adults. As of the interim analysis (data cutoff date: 25 January 2025), the RP2D had been established for Cohorts 1 and 2 at the weight-equivalent of a 45-mg dose in adults.

5.3.2. Main study: INCB 84344-102

5.3.2.1.1. Study title

An Open-Label, Single-Arm, Phase 1/2 Study Evaluating the Safety and Efficacy of Ponatinib for the Treatment of Recurrent or Refractory Leukemias or Solid Tumors in Paediatric Participants

5.3.2.1.2. Study design

Study INCB 84344-102 is an ongoing open-label, single-arm, Phase 1/2 study evaluating the safety and efficacy of ponatinib in monotherapy for the treatment of R/R leukemias, lymphomas, or solid tumors in paediatric participants. The study consists of 2 parts.

Phase 1 (completed) was a run-in phase for dose finding of the MTD/RP2D of ponatinib for paediatric participants with advanced leukaemias, lymphomas, or solid tumors for which standard therapy is not available or is not indicated. Phase 1 was conducted in a staggered approach, in 3 age defined cohorts, using a rolling-6 design:

- Cohort 1: ≥ 12 to < 18 years old
- Cohort 2: ≥ 6 to < 12 years old
- Cohort 3: ≥ 1 to < 6 years old

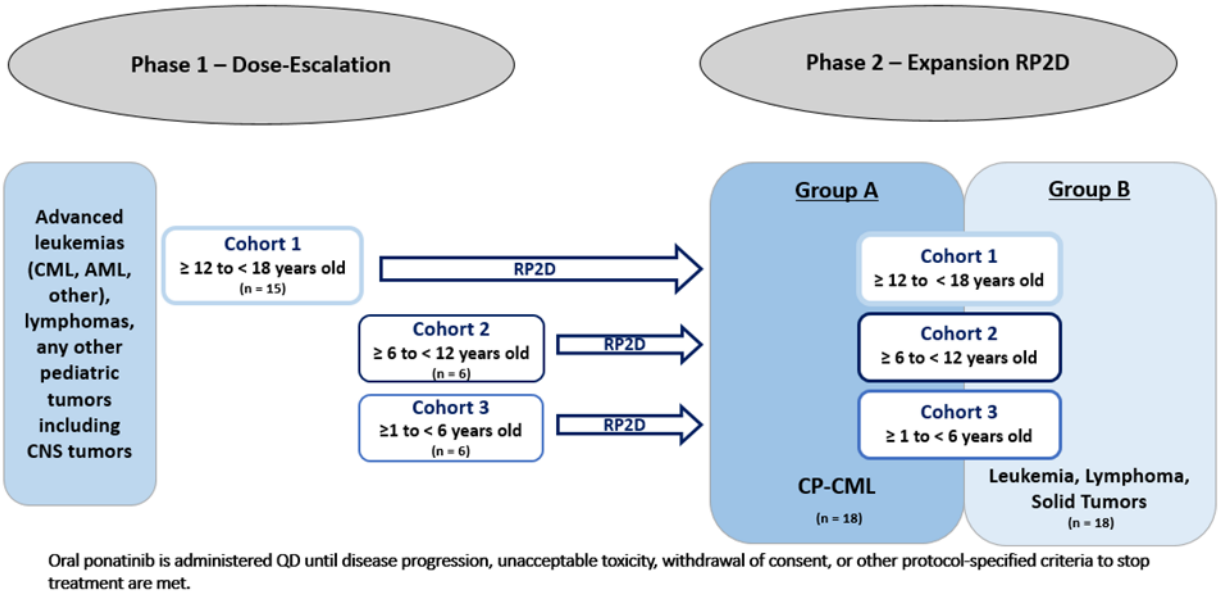
Phase 2 (ongoing) includes a dose expansion with up to a total of approximately 36 participants aged ≥ 1 and < 18 years (18 participants in each expansion group). The study expansion was initiated once the RP2D and safety data were available for each Phase 1 cohort, and the Data Safety Monitoring Board provided agreement to start the expansion phase. The expansion groups include the following:

- Group A (CP-CML): A standard, single-arm, Phase 2 design to evaluate the activity of ponatinib monotherapy in paediatric participants with CP-CML who are resistant to or intolerant of at least 1 prior BCR-ABL–targeted TKI therapy or who have the kinase domain mutation T315I.

- Group B (other tumors): A standard, single-arm, Phase 2 design to evaluate the activity of ponatinib monotherapy in paediatric participants with select advanced leukemias, lymphomas, or solid tumors.

Only the Phase 2 Group A (CP-CML) is assessed in this procedure.

Figure 11: INCB 84344-102 Study Design



Source: INCB 84344-102 CSR Figure 1.

5.3.2.1.2.1. Treatment

Table 1: Starting Dose for Cohorts 1 and 2 in Phase 2

Cohort 1 and Cohort 2[a]	Ponatinib Starting Dose[b]
Participants weighing ≥ 45 kg	45 mg/day
Participants weighing ≥ 30 to < 45 kg	30 mg/day
Participants weighing ≥ 15 to < 30 kg	15 mg/day
Participants weighing ≥ 5 to < 15 kg	5 mg/day

[a] Cohort 1 = participants ≥ 12 to < 18 years old and Cohort 2 = participants ≥ 6 to < 12 years old.
[b] Based on 45-mg adult dose allometric scaling.

Source: Protocol INCB 84344-102

Participants in Phase 2 received study treatment until treatment failure (including progression of disease or requiring additional systemic anticancer therapy), unacceptable toxicity, or death.

For participants from Phase 2 with CP-CML (Group A) only, the dose of study treatment was recommended to be reduced according to investigator's judgment to the adult-equivalent dose of 15 mg QD based on the participant's body weight, for participants who achieved a MCyR and taking the following factors into account in the individual participant assessment: cardiovascular risk, side effects of study treatment, time to cytogenetic response, and BCR-ABL transcript levels.

5.3.2.1.2.2. Randomisation and blinding

Not applicable. This is a single-arm and open-label trial.

5.3.2.1.2.3. Patient population

Paediatric participants (aged ≥ 1 to < 18 years), with advanced leukemias, lymphomas, or solid tumors were enrolled in this study.

Key Inclusion criteria for Phase 2, Group A with CP-CML

Diagnosis

- Histologically or cytologically confirmed diagnosis of CP-CML at the time of study entry and must be resistant to or intolerant of at least 1 prior BCR-ABL–targeted TKI therapy or have the T315I kinase domain mutation or be in "warning" response status (*Table 11*). Warning response status must a) be confirmed by at least 2 assessments performed at least 1 month apart and b) justify the change of treatment by comorbidities and tolerability.

Table 2: Definition of the response to TKIs (any TKI) as First-Line Treatment

Timepoint	Optimal	Warning	Failure
Baseline	NA	High risk or CCA/Ph+, major route	NA
3 months	BCR-ABL1 ≤ 10% and/or Ph+ ≤ 35%	BCR-ABL1 > 10% and/or Ph+ 36%-95%	Non-CHR and/or Ph+ > 95%
6 months	BCR-ABL1 < 1% and/or Ph+ 0	BCR-ABL1 1%-10% Ph+ 1-35%	BCR-ABL1 > 10% and/or Ph+ > 35%
12 months	BCR-ABL1 ≤ 0.1%	BCR-ABL1 > 0.1%-1%	BCR-ABL1 > 1% and/or Ph+ > 0
Then, and at any time	BCR-ABL1 ≤ 0.1%	CCA/Ph– (–7, or 7q–)	Loss of CHR Loss of CCyR Confirmed loss of MMR[a] Mutations CCA/Ph+

NA = Not Applicable; MMR = BCR-ABL1 ≤ 0.1% = $MR^{3.0}$ or better; CCA/Ph+ = clonal chromosome abnormalities in Ph+ cells; CCA/Ph^- = clonal chromosome abnormalities in Ph^- cells.
Note: The definitions are the same for the patients in CP, AP, and PB and apply also to second-line treatment, when first-line treatment was changed for intolerance. The response can be assessed with either a molecular or a cytogenetic test, but both are recommended whenever possible. Cutoff values have been used to define the boundaries between optimal and warning, and between warning and failures.
[a] In 2 consecutive tests, of which one with a BCR-ABL1 transcripts level ≥ 1%.
Source: Baccarani et al 2013.

- Must have 1 bone marrow aspirate with documentation of BCR-ABL translocation by conventional cytogenetics, metaphase FISH, or q-PCR performed within 42 days before the first dose of ponatinib.

Prior therapies

- Participants who are resistant to or intolerant of at least 1 prior BCR-ABL–targeted TKI therapy (exception for participants with T315I mutation) or are in warning status (.

Performance level

- Karnofsky performance status ≥ 40% for participants ≥ 16 years old or Lansky Play Scale ≥ 40% for paediatric participants < 16 years old.

Key Exclusion criteria for Phase 2, Group A with CP-CML

Participants are excluded from the study if any of the following criteria apply:

Prior therapies

- Participants who have had cytotoxic chemotherapy within 21 days (or 42 days for nitrosoureas or mitomycin C) before the first dose of ponatinib.
- Autologous or allogeneic stem cell transplant < 3 months before the first dose of ponatinib.
- Prior treatment with any of the following:

– Immunosuppressive therapy (including post stem cell transplant regimens) within 14 days before the first dose of ponatinib.

– Any targeted cancer therapy (including TKIs) within 7 days before the first dose of ponatinib.

– Any other investigational anticancer agents within 30 days or 5 half-lives, whichever is longer, before first dose of ponatinib.

– Any biotherapeutic (including monoclonal antibody–directed) anticancer therapy within 5 half-lives or 30 days whichever is shorter, before the first dose of ponatinib.

– Any chimeric antigen receptor therapy within 28 days before the first dose of ponatinib

– Ponatinib

Renal and Hepatic Function

- Calculated creatinine clearance per Schwartz Formula (estimated GFR [mL/min/1.73 m2] = k × height [cm] / serum creatinine [mg/dL], where k = 0.413) or radioisotope glomerular filtration rate < 70 mL/min/1.73 m2
- Patient's AST and ALT ≥5 x ULN for age (unless related to leukemic involvement)

Cardiac Function

- SF < 27% by ECHO, OR EF < 50% by MUGA.
- Abnormal QTcF on screening ECG, defined as QTcF of ≥ 450 ms.

5.3.2.1.3. Objectives and estimands

5.3.2.1.3.1. Primary objective

The objective of Phase 1 was to determine the MTD and/or RP2D of oral ponatinib administered QD in paediatric participants with selected advanced hematologic malignancies or solid tumors.

The primary objective of Group A (CP-CML) Phase 2 was to determine the efficacy of oral ponatinib administered QD in paediatric participants with CP-CML who are resistant or intolerant to at least 1 prior BCR-ABL–targeted TKI therapy or who have the T315I mutation.

5.3.2.1.3.2. Estimand for the primary objective

Efficacy was to be assessed in participants from Phase 2 who were administered ponatinib at the RP2D. The IA for this study included primary and key secondary efficacy endpoints. Phase 1 of the study did not include a primary efficacy endpoint.

Primary Efficacy Endpoints

The primary efficacy endpoint for participants with CP-CML in Phase 2 is major cytogenic response (MCyR) by (within) 12 months, defined as complete cytogenic response (CCyR) or partial cytogenic response (PCyR) by (within) 12 months, assessed by conventional cytogenetics or FISH. For MCyR by (within) 12 months, the best cytogenetic response will be considered. A participant will be considered a responder if they have a best cytogenetic response of CCyR or PCyR by 12 months.

Key Secondary Efficacy Endpoints

For participants in Phase 2 with CP-CML, the secondary endpoints include complete haematologic response (CHR) at 6 months, CCyR at 12 months, MMR at 12 months, time to response, DoR, PFS, and OS.

Table 3: Assessment of response

CHR (Complete haematological response)	
WBC count $< 10\times10^9$/L	
No immature granulocytes	
Basophils < 5%	
Platelet count $< 450\times10^9$/L	
Spleen non-palpable	
Cytogenetic response (CyR)	
Complete CyR	No Ph+ metaphases by CBA, or < 1% BCR–ABL+ nuclei by iFISH out of ≥ 200 cells
Partial CyR	1%–35% Ph+ metaphases by CBA
Minor CyR	36%–65% Ph+ metaphases by CBA
Minimal CyR	66%–95% Ph+ metaphases by CBA
No CyR	> 95% Ph+ metaphases by CBA
Molecular response (MR)	
Major MR (MMR)	BCR–ABL transcript level ≤ 0.1% on the International Scale
Deep MR:	
MR^4	BCR–ABL transcript level ≤ 0.01% on the International Scale or BCR–ABL not detectable with at least 10 000 ABL or 24 000 GUS transcripts
$MR^{4.5}$	BCR–ABL transcript level ≤ 0.0032% on the International Scale or BCR–ABL not detectable with at least 32 000 ABL or 77 000 GUS transcripts

CBA, chromosome banding analysis; iFISH, interphase fluorescent *in situ* hybridisation; Ph, Philadelphia; WBC, white blood cell.

Source: Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2017.

Statistical methods for estimation and sensitivity analysis on primary estimand

Descriptive summaries, including the numbers and percentages of participants in the indication specific Full Analysis Set (FAS), are provided for all the primary endpoints in Phase 2, with the corresponding 95% CIs calculated based on the exact methods for binomial distributions. Data have been summarized overall and by treatment cohort based on the initially assigned dose. No formal statistical comparison analysis was planned for this study.

The FAS included all participants enrolled in the study who received at least 1 dose of ponatinib treatment. The FAS was used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all safety, study treatment administration. The FAS also includes indication-specific subsets of participants used for efficacy analysis (FAS with CP-CML, FAS with other leukemias, FAS with lymphoma FAS with solid tumor, and FAS with other BCR-ABL-positive leukemias [AP/BL-CML and Ph+ ALL]). The PK-Evaluable Population consists of all enrolled participants who received at least 1 dose of study treatment and provided at least 1 postdose sample for PK analysis. The dose-limiting toxicity (DLT)-Evaluable Population consisted of all participants meeting the definition of DLT-evaluable as defined per Protocol and was used in the establishment of tolerable ponatinib dose

All the analyses in this study (including those for this IA) are of a descriptive nature, with no formal statistical comparisons planned. This IA includes analyses of the primary and key secondary endpoints and additional selected exploratory translational endpoints.

The primary endpoint for Phase 1 of the study used the DLT-Evaluable Population for the identification of an MTD and establishment of the RP2D. The primary endpoint for the Phase 2 of the study was specific for each indication-specific population and included Phase 2 participants dosed at RP2D.

5.3.2.1.4. Results

Only results relevant for the applied indication are included, i.e. results for patients with CP-CML.

5.3.2.1.5. Participant flow and numbers analysed

In the overall study population, all 11 participants (100.0%) with CP-CML had received at least 1 dose of ponatinib, 8 participants (72.7%) were still on treatment, and 3 (27.3%) had discontinued treatment. None of the participants had completed treatment. All participants were still in the study at the time of data cutoff; none had completed or withdrawn from study. Of the 3 participants who had discontinued treatment, 2 discontinued due to AEs and 1 discontinued due to the investigator's decision.

Table 4: Summary of Participant Disposition (Full Analysis Set with CP-CML)

Variable	Phase 1	Phase 2[a]		Total (N = 11)
	Cohort 2 DL 1 (≥ 6 to < 12 y) (N = 1)	Cohort 1 (≥ 12 to < 18 y) (N = 8)	Cohort 2 (≥ 6 to < 12 y) (N = 2)	
Number (%) of participants treated	1 (100.0)	8 (100.0)	2 (100.0)	11 (100.0)
Number (%) of participants with ongoing treatment	1 (100.0)	5 (62.5)	2 (100.0)	8 (72.7)
Number (%) of participants who discontinued treatment	0 (0.0)	3 (37.5)	0 (0.0)	3 (27.3)
Primary reason				
AE	0 (0.0)	2 (25.0)	0 (0.0)	2 (18.2)
Physician decision	0 (0.0)	1 (12.5)	0 (0.0)	1 (9.1)
Number (%) of participants still in the study	1 (100.0)	8 (100.0)	2 (100.0)	11 (100.0)

[a] Group A.

The first participant was dosed 29 January 2020. Data cutoff date was 25 January 2025. At the time of this assessment, the study was still recruiting. Patients in Phase 2, with CML were recruited from Italy (n=8), France (n=1) and the Netherlands (n=1).

5.3.2.1.5.1. Deviations from study plan

There were three protocol amendments. Only major protocol amendments concerning Phase 2, Group A (CP-CML) are listed:

Amendment 1 (issued on 06 May 2021)

- Text has been added to indicate that an interim analysis will be performed.

Amendment 2 (issued on 16 January 2023)

- Inclusion Criteria (Criteria 1b and 2b) Description of change: Inclusion Criteria were updated to specify the criteria of a warning response status (refer to *Table 11*).

Amendment 3 (issued on 20 February 2025)

- For Group A (CP-CML), the minimum of 3 participants per age-cohort was removed
- Inclusion Criterion 1b was updated to include participants in Phase 2, Group A who are in "warning" response status. As a result, Exclusion Criterion 1 was removed.

5.3.2.1.5.2. Baseline data

In the Phase 2 CP-CML population, the median age was 14.0 years (range: 11-17 years). The proportion of females and males was equal. The majority of participants were white (90%).

All participants (100.0%) with CP-CML had received prior BCR-ABL TKI treatment.

Table 5: Summary of Demographic and Baseline Characteristics of paediatric participants with CP-CML in Study 102

Variable	Total (N = 10)
Age (years)	
Mean (SD)	13.9 (2.23)

Variable	Total (N = 10)
Median (Min, Max)	14.0 (11, 17)
Sex - n (%)	
Male	5 (50.0)
Female	5 (50.0)
Race - n (%)	
White/Caucasian	9 (90.0)
Not Reported	1 (10.0)
Ethnicity - n (%)	
Not Hispanic or Latino	9 (90.0)
Not Reported	1 (10.0)
Weight (kg) at baseline	
Mean (SD)	52.84 (15.75)
Median (Min, Max)	57.75 (25.0, 72.0)
Height (cm) at baseline	
Mean (SD)	158.6 (17.09)
Median (Min, Max)	161.0 (125, 179)
BMI (kg/m^2) at baseline	
Mean (SD)	20.48 (3.817)
Media (Min, Max)	21.11 (13.8, 25.6)

Efficacy is presented for the 10 participants in the FAS with CP-CML subset in Phase 2. Phase 1 of the study did not include a primary efficacy endpoint.

5.3.2.1.5.3. Outcomes and estimation

Primary Efficacy Endpoints

In the CP-CML population, at the time of the IA data cutoff, the MCyR rate by 12 months was 90% (9 out of 10 participants [95% CI: 55.50, 99.75]). All participants with an MCyR had a CCyR.

One of the participants who achieved MCyR had their dose reduced to the weight-equivalent of a 15-mg dose in adults as allowed per Protocol. The participant was still in response at the time of the IA data cutoff.

Table 6: Study INCB 84344-102: Summary of Cytogenetic Response and Major Cytogenetic Response Rate by 12 Months (Full Analysis Set With CP-CML in Phase 2)

Variable	Phase 2		Total (N = 10)
	Cohort 1 (≥ 12 to < 18 y) (N = 8)	Cohort 2 (≥ 6 to < 12 y) (N = 2)	
Best cytogenetic response by 12 mo[a], n (%)			
Major (MCyR)	7 (87.5)	2 (100.0)	9 (90.0)
Complete (CCyR)	7 (87.5)	2 (100.0)	9 (90.0)
Minimal	1 (12.5)	0 (0.0)	1 (10.0)
Major cytogenetic response by 12 mo[a], n (%)	7 (87.5)	2 (100.0)	9 (90.0)
95% CI for response rate[b]	47.35, 99.68	15.81, 100.00	55.50, 99.75

Note: Cytogenetic response was assessed by conventional cytogenetics or FISH.
[a] For "by 12 months," the best cytogenetic response was determined in the order of CCyR, PCyR, minor, minimal, none. Any assessments after new anticancer therapy were excluded from the best response.
[b] Confidence intervals were calculated based on exact methods for binomial distribution.
Source: Table 2.1.1.

Key Secondary Endpoints

Hematologic Response

For participants in Phase 2 with CP-CML, the CHR rate at 6 months was 90.0% (95% CI: 55.50, 99.75), with 9 out of 10 participants with CP-CML having a CHR. One participant discontinued treatment after approximately 4 months and therefore no assessments were available for this participant at 6 months.

Table 7: Study INCB 84344-102: Summary of Hematologic Response and Complete Hematologic Response Rate at 6 Months (Full Analysis Set With CP-CML in Phase 2)

Variable	Phase 2		Total (N = 10)
	Cohort 1 (≥ 12 to < 18 y) (N = 8)	Cohort 2 (≥ 6 to < 12 y) (N = 2)	
Hematologic response at 6 months, n (%)			
CHR	7 (87.5)	2 (100.0)	9 (90.0)
Not assessed[a]	1 (12.5)	0 (0.0)	1 (10.0)
CHR at 6 months[b], n (%)	7 (87.5)	2 (100.0)	9 (90.0)
95% CI for response rate[c]	47.35, 99.68	15.81, 100.00	55.50, 99.75

[a] No postbaseline response at 6 months was available.
[b] If all participants had "not assessed" as response, the response rate was calculated as "not estimable".
[c] Confidence intervals were calculated based on exact methods for binomial distribution.
Source: INCB 84344-102 CSR Table 22.

Cytogenetic Response

For participants in Phase 2 with CP-CML, the MCyR rate at (exactly the time point 12 months) 12 months was 50.0% (95% CI: 18.71, 81.29). All 5 participants who had a response had a CCyR. Five participants were not assessed as they did not have assessments available at this timepoint (2 participants had discontinued from treatment and their last available assessment was at 3 months and at 9 months, respectively; 3 participants were still on treatment, but 2 participants had a missing

assessment for CyR at 12 months and 1 participant's 12-month assessment was to occur after the data cutoff date).

Responses were observed at 3 months (MCyR rate was 60.0%; 6 participants had a CCyR, 1 participant had a minimal response, and 3 participants were not assessed), and they steadily increased over time at 6 and 9 months (80.0% and 90.0%, respectively).

Note that at any given timepoint, if an assessment was missing, the participant was considered a nonresponder.

Table 8: Study INCB 84344-102: Summary of Cytogenetic Response and Complete Cytogenetic Response Rate at 12 Months (Full Analysis Set With CP-CML in Phase 2)

Variable	Phase 2		Total (N = 10)
	Cohort 1 (≥ 12 to < 18 y) (N = 8)	Cohort 2 (≥ 6 to < 12 y) (N = 2)	
CyR at 12 months, n (%)			
MCyR	4 (50.0)	1 (50.0)	5 (50.0)
CCyR	4 (50.0)	1 (50.0)	5 (50.0)
Not assessed[a]	4 (50.0)	1 (50.0)	5 (50.0)
CCyR at 12 months[b], n (%)	4 (50.0)	1 (50.0)	5 (50.0)
95% CI for response rate[c]	15.70, 84.30	1.26, 98.74	18.71, 81.29

[a] No postbaseline response at 12 months was available.
[b] If all participants had "not assessed" as response, the response rate was calculated as "not estimable".
[c] Confidence intervals were calculated based on exact methods for binomial distribution.
Source: INCB 84344-102 CSR Table 23.

The median time to CyR was 0.99 months (95% CI: 0.95, 1.02; see Table 19). Nine participants achieved MCyR and 1 participant was censored due to the start of a new anticancer treatment at the time of the last valid assessment.

Table 9: Study INCB 84344-102: Summary of Time to Cytogenetic Response (Full Analysis Set With CP-CML in Phase 2)

Variable	Phase 2		Total (N = 10)
	Cohort 1 (≥ 12 to < 18 y) (N = 8)	Cohort 2 (≥ 6 to < 12 y) (N = 2)	
Number (%) of participants with events	7 (87.5)	2 (100.0)	9 (90.0)
MCyR	7 (87.5)	2 (100.0)	9 (90.0)
Number (%) of participants censored	1 (12.5)	0 (0.0)	1 (10.0)
Median time to CyR, months (95% CI)[a]	0.97 (0.95, 2.73)	0.99 (NE, NE)	0.99 (0.95, 1.02)

[a] Confidence intervals were calculated based on the Brookmeyer and Crowley (1982) method.
Source: INCB 84344-102 CSR Table 24.

Duration of CyR was derived for participants who achieved an MCyR. The median DoR had not been reached at the time of the IA. All participants were censored (8 participants were still in response and censored at their last valid assessment, and 1 participant had started a new anticancer treatment and was censored at the last valid assessment before new anticancer therapy initiated). The median follow-up time was 15.57 months (95% CI: 4.40, 32.23).

Molecular Response

For participants in Phase 2 with CP-CML, the MMR rate (MR3, defined as ≤ 0.1% *BCR ABL1*^{IS}, or better) at 12 months was 60.0% (95% CI: 26.24, 87.84). At 12 months, 4 participants (40.0%) had achieved MMR (or MR3) and 2 participants (20.0%) had achieved MR4-5. Assessments at 12 months were not available for 4 participants (3 participants had discontinued treatment and 1 participant was still on treatment, but the 12-month assessment was to occur after the data cutoff date.

Table 20: Study INCB 84344-102: Molecular Response and Major Molecular Response Rate at 12 Months (Full Analysis Set With CP-CML in Phase 2)

Variable	Phase 2		Total (N = 10)
	Cohort 1 (≥ 12 to < 18 y) (N = 8)	Cohort 2 (≥ 6 to < 12 y) (N = 2)	
MR at 12 months, n (%)			
MR4-5	2 (25.0)	0 (0.0)	2 (20.0)
MR3 (MMR)	3 (37.5)	1 (50.0)	4 (40.0)
Not assessed[a]	3 (37.5)	1 (50.0)	4 (40.0)
MMR at 12 months[b], n (%)	5 (62.5)	1 (50.0)	6 (60.0)
95% CI for response rate[c]	24.49, 91.48	1.26, 98.74	26.24, 87.84

Note: Results at a specific timepoint provide noncumulative data for that timepoint.
[a] No postbaseline response at 12 months was available.
[b] If all participants had "not assessed" as response, the response rate was calculated as "not estimable".
[c] Confidence intervals were calculated based on exact methods for binomial distribution.
Source: INCB 84344-102 CSR Table 25.

The median time to MR was 2.83 months (95% CI: 1.02, NE). Eight participants achieved MMR. Of the 2 censored participants, 1 was censored due to absence of response at their last valid assessment, and 1 was censored at the last valid assessment before new anticancer treatment was initiated.

Duration of MR was derived for the 8 participants who achieved MMR. The median DoR had not been reached at the time of the IA. The median follow-up time was 24.77 months (95% CI: 11.07, NE). Three participants had lost their responses while 5 participants were censored as they had not lost their MMR at their last valid assessment.

Table 10: Study INCB 84344-102: Summary of Duration of Molecular Response (Full Analysis Set With CP-CML in Phase 2)

Variable	Phase 2		Total (N = 10)
	Cohort 1 (≥ 12 to < 18 y) (N = 8)	Cohort 2 (≥ 6 to < 12 y) (N = 2)	
Number (%) of participants with MMR	6 (75.0)	2 (100.0)	8 (80.0)
Number (%) of participants with events	2 (25.0)	1 (50.0)	3 (30.0)
Loss of MMR	2 (25.0)	1 (50.0)	3 (30.0)
Number (%) of participants censored	4 (50.0)	1 (50.0)	5 (50.0)
Median duration of MR, months (95% CI)[a]	NE (1.64, NE)	NE (5.59, NE)	NE (1.64, NE)
Kaplan-Meier estimates (95% CI) of DoR			
3 Months	66.7 (19.5, 90.4)	100.0 (100.0, 100.0)	75.0 (31.5, 93.1)
6 Months	66.7 (19.5, 90.4)	50.0 (0.6, 91.0)	62.5 (22.9, 86.1)
9 Months	66.7 (19.5, 90.4)	50.0 (0.6, 91.0)	62.5 (22.9, 86.1)
12 Months	66.7 (19.5, 90.4)	NE (NE, NE)	62.5 (22.9, 86.1)

Variable	Phase 2		Total (N = 10)
	Cohort 1 (≥ 12 to < 18 y) (N = 8)	Cohort 2 (≥ 6 to < 12 y) (N = 2)	
Median follow-up time[b], months (95% CI)	24.82 (13.80, NE)	11.07 (NE, NE)	24.77 (11.07, NE)

Note: Duration of molecular response was derived only for participants with MMR.
[a] Confidence intervals were calculated based on the Brookmeyer and Crowley (1982) method.
[b] Median follow-up time was estimated using a reverse Kaplan-Meier method by reversing censoring and event.
Source: INCB 84344-102 CSR Table 27.

Progression-Free Survival

For participants in Phase 2 with CP-CML, the median PFS for CyR had not been reached at the time of the IA. The probability of remaining progression free at 3, 6, 9, and 12 months was estimated as 100.0% for each timepoint. All 10 participants were censored (8 participants were still in response at their last valid assessment and 2 were censored at the last valid assessment before initiating new anticancer therapy initiated). The median follow-up time was 15.16 months (95% CI: 2.76, 27.53).

Similarly, the median PFS for MR was not reached at the time of the IA. The probability of remaining progression free at 3, 6, 9, and 12 months was estimated as 88.9%, 88.9%, 66.7%, and 66.7%, respectively. The median follow-up time was 16.56 months. Three participants had events of loss of response while 7 were censored (6 participants were still in response at their last valid assessment and 1 had started a new anticancer treatment). Of the 3 participants with loss of response, 2 participants had a loss of response before the 9-month assessment, and 1 participant discontinued treatment after the 3-month assessment and before the 6-month assessment.

Table 11: Study INCB 84344-102: Summary of Progression-Free Survival of Molecular Response (Full Analysis Set With CP-CML in Phase 2)

Variable	Phase 2		Total (N = 10)
	Cohort 1 (≥ 12 to < 18 y) (N = 8)	Cohort 2 (≥ 6 to < 12 y) (N = 2)	
Number (%) of participants with events	2 (25.0)	1 (50.0)	3 (30.0)
Loss of MMR	2 (25.0)	1 (50.0)	3 (30.0)
Number (%) of participants censored	6 (75.0)	1 (50.0)	7 (70.0)
Median PFS, months (95% CI)[a]	NE (2.79, NE)	NE (8.34, NE)	NE (2.79, NE)
Kaplan-Meier estimates (95% CI) of PFS of MR			
3 Months	85.7 (33.4, 97.9)	100.0 (100.0, 100.0)	88.9 (43.3, 98.4)
6 Months	85.7 (33.4, 97.9)	100.0 (100.0, 100.0)	88.9 (43.3, 98.4)
9 Months	71.4 (25.8, 92.0)	50.0 (0.6, 91.0)	66.7 (28.2, 87.8)
12 Months	71.4 (25.8, 92.0)	50.0 (0.6, 91.0)	66.7 (28.2, 87.8)
Median follow-up time, months[b] (95% CI)	27.53 (2.76, NE)	16.53 (NE, NE)	16.56 (2.76, 33.15)

[a] Confidence intervals were calculated based on the Brookmeyer and Crowley (1982) method.
[b] Median follow-up time was estimated using a reverse Kaplan-Meier method by reversing censoring and event.
Source: INCB 84344-102 CSR Table 28.

Overall Survival

No deaths were reported for this population at the time of the IA.

5.3.3. Clinical studies in special populations

N/A

5.3.4. Study - Ponatinib-1501

Study Ponatinib-1501 (ponatinib in Combination with Chemotherapy in paediatric Participants with Ph+ ALL) has been submitted in this application, in compliance with the agreed PIP. No paediatric indication in Ph+ ALL has been requested by the MAH.

Ponatinib-1501 was a Phase 1/2, single-arm, open-label, multicenter study designed to evaluate the safety, tolerability, PK, and efficacy of ponatinib when administered in combination with multiagent chemotherapy in paediatric patients with Ph+ ALL, Ph+ MPAL, or Ph-like ALL who had a relapse, were resistant or intolerant to at least 1 prior BCR-ABL1 TKI therapy, or had the T315I mutation. The study was terminated early due to observed toxicities.

The study consisted of the following 2 parts:

- Phase 1: a PK/safety lead-in phase for dose confirmation to establish the RP2D of ponatinib in combination with a chemotherapy backbone
- Phase 2: to evaluate the efficacy and safety of ponatinib at the RP2D in combination with chemotherapy in the study population

Study Population

In Study Ponatinib-1501, the Response-Evaluable Population was to be composed of participants with Ph+ ALL administered ponatinib at the RP2D. No analyses were performed on the Response-Evaluable Population because the RP2D could not be established. Efficacy was assessed in those participants who received at least 1 dose of ponatinib during Phase 1 of the study. In total, 11 participants (7 in Cohort 1 and 4 in Cohort 2) were enrolled at 9 sites during Phase 1:

- Ponatinib was administered to 7 participants in Cohort 1 at the 30 mg QD adult equivalent dose. After 5 eligible participants were enrolled, there were no reported DLTs at the time and 2 more participants were enrolled; it was agreed to by the sponsor to continue enrollment of participants younger than 16 years of age to fulfill the PK evaluation.
- Ponatinib was administered to 4 participants in Cohort 2 at the 15 mg QD adult equivalent dose.

Enrollment into Phase 1 was closed after 2 participants in Cohort 2 had DLTs. The RP2D was not established, and Phase 2 was not initiated. The study was terminated on 19 JUL 2024.

Six participants completed the reinduction block, 6 participants completed the consolidation block, and 5 participants received optional ponatinib continuation therapy. One of the 11 participants was reported to have completed study treatment.

Participants in this study were aged $\geq$ 1 to $\leq$ 21 years with Ph+ ALL, Ph+ MPAL, or Ph-like ALL with targetable kinase-activating lesions who had a relapse, were resistant or intolerant to at least 1 prior therapy that contained a BCR-ABL1-targeted TKI, or had a BCR ABL1 T315I mutation. At baseline, the median age was 12.0 years (range: 9-17 years) in Cohort 1 and 13.0 years (range: 10-18 years) in Cohort 2. More than half of the participants were female (54.5%) and more than half were Asian.

All participants received prior TKIs; 7 participants received imatinib (first-generation TKI), and 7 participants received dasatinib (second-generation TKI). One participant received 1 line of prior

chemotherapy, and 10 participants received 2 lines of prior chemotherapy. Most participants (8 of 11 [72.7%]) had CR while receiving the last prior anticancer therapy.

Summary of Key Efficacy Results

The secondary efficacy endpoint for Phase 1 was CR at the end of the reinduction block, which consisted of the first 35-day block of study therapy. Three participants had CR at the end of the reinduction block per Protocol definition, including 1 participant in Cohort 1 (ponatinib 30 mg adult-equivalent) and 2 participants in Cohort 2 (ponatinib 15 mg adult equivalent).

All participants with a bone marrow assessment available had clearance of the blasts (< 5% or undetectable) from their bone marrow during the study. Among 9 participants with evaluable bone marrow at the end of the reinduction block (6 participants in Cohort 1 and 3 participants in Cohort 2), all had a reduction in blasts in the bone marrow (< 5%). However, only 4 participants had hematologic recovery of their platelet and neutrophil counts. Of the 6 participants who completed the consolidation block, 2 of 5 participants in Cohort 1 and 0 of 1 participant in Cohort 2 had CR per Protocol at the end of the block. No participants had a relapse from CR at the end of the consolidation block or at the EOT visit. No deaths were reported during the study, and the median follow-up for OS was 23.8 months (95% CI: 18.5, 38.5) in Cohort 1 and 7.9 months (95% CI: 3.5, not estimable) in Cohort 2.

Efficacy Conclusions

In study Ponatininb-1501, paediatric participants with R/R Ph+ ALL were treated with ponatinib in combination with an intensive 4-drug induction chemotherapy regimen.

Due to the observed toxicities, no tolerable dose could be identified.

5.3.5. Analysis performed across trials (pooled analyses and meta-analysis)

N/A

5.3.6. Overall discussion and conclusions on clinical efficacy

5.3.6.1. Discussion

Ponatinib Monotherapy in paediatric Participants With CP-CML, Other Leukemias, or Solid Tumors (Study INCB 84344-102)

Study INCB 84344-102 is an ongoing phase I/II, single-arm, open-label study to determine the safety and efficacy of ponatinib in paediatric patients with recurrent or refractory leukemias or solid tumors.

In the CP-CML population, the median age was 14.0 years (range: 11-17 years). The proportion of females and males was equal. All participants had received prior BCR-ABL TKI treatment.

Efficacy was to be assessed in participants with CP-CML who were administered ponatinib at the RP2D (n=10, included only participants in phase 2).

The primary endpoint, MCyR rate by 12 months, was achieved by 90% (9 out of 10 participants [95% CI: 55.50, 99.75]), meaning that 90% had responded at some point before or up to 12 months. All participants with an MCyR had a CCyR.

The MMR rate (MR3, defined as ≤ 0.1% *BCR ABL1*^{IS}, or better) at 12 months was 60.0% (95% CI: 26.24, 87.84).

The median PFS for molecular response (MR) was not reached at the time of the IA. The median follow-up time was 16.6 months. Three participants had events of loss of response while 7 were censored (6 participants were still in response at their last valid assessment and 1 had started a new anticancer treatment). No deaths were reported for this population at the time of the IA.

The MAH initially applied for the approval of the indication "in paediatric patients 6 years of age or older with chronic phase chronic myeloid leukaemia (CP-CML) who are resistant or intolerant to at least one tyrosine kinase inhibitor."

The effectiveness of ponatinib is already demonstrated in adults. The approach to establishing the effectiveness of ponatinib for paediatric use is a PK bridging approach from adults. The PK bridging is supported by limited clinical data in children from study INCB 84344-102. This strategy was endorsed in a CHMP scientific advice.

CML in children is considered to be biologically similar to CML in adults. Both paediatric and adult CML are driven by the same BCR-ABL fusion gene, leading to similar underlying pathophysiology and disease progression mechanisms. Because of this biological similarity, the mode of action of targeted treatments is expected to be the same across age groups.

Therefore, efficacy data generated in adults can be extrapolated to support paediatric indications for CML. This extrapolation is scientifically justified by the shared molecular mechanism, comparable treatment objectives, and similar clinical response patterns observed between adults and children. The extrapolation is complemented by paediatric pharmacokinetic as well as limited efficacy and safety studies, which confirm that children achieve similar systemic exposure and tolerability at appropriately adjusted doses.

The approved indication for CML in adults is: "chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (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".

Given that the sought paediatric extension of indication is determined by extrapolation of efficacy and safety from the adult patient population, the proposed use would need to be similar to that which is approved in adults based on the efficacy and safety database to which PK bridges. The limited paediatric data does not alone support the use of ponatinib as a second line treatment, which was suggested by the MAH's proposed indication for children "who are resistant or intolerant to at least one tyrosine kinase inhibitor".

Therefore, the initially proposed indication from the MAH was not accepted and, following a request from the CHMP, the proposed paediatric indication in CP-CML was amended in line with the approved indication in adults, as follows:

"Iclusig is indicated as monotherapy in paediatric patients 6 years of age or older with chronic phase chronic myeloid leukaemia (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."

Ponatinib in Combination with Chemotherapy in paediatric Participants with Ph+ ALL (Study Ponatinib-1501)

The MAH has submitted the primary analysis results of paediatric study Ponatinib-1501. The study was terminated early due to observed toxicities, and the MAH considers that the submitted study results do not support a paediatric indication. The MAH proposes an update of the SmPC section 5.1 to include the results from study Ponatinib-1501. The proposed update of the SmPC is accepted.

5.3.6.2. Conclusions on the clinical efficacy

The approach to establishing the effectiveness of ponatinib for paediatric use in CP-CML is a PK bridging approach from adults. The PK bridging is supported by limited clinical data in children (Study INCB 84344-102).

This extrapolation is scientifically justified by the shared molecular mechanism of disease, a targeted therapy against the molecular driver of disease, comparable treatment objectives, and similar clinical response patterns observed between adults and children. The extrapolation is complemented by paediatric pharmacokinetic as well as limited efficacy and safety studies, which confirm that children achieve similar systemic exposure and tolerability at appropriately adjusted doses. This is supported by EMA guidance (EMEA/CHMP/EWP/147013/2004) and precedents.

5.4. Clinical safety

Please refer to the table of studies in section 5.3.2.

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The safety data in support of this application derive from the interim analysis of the Phase 1/2 Study INCB 84344-102 (ongoing, data cutoff date: 25 Jan 2025) including 61 participants enrolled in the study who received at least 1 dose of ponatinib (Overall population, FAS). The CP-CML expansion cohort, a subset of the FAS, included (11) participants in the study with CP-CML, from Phase 1 (1 participant) and Phase 2 (10 participants) combined.

The MAH provided supportive safety results of ponatinib treatment in combination with chemotherapy in paediatric participants with R/R Ph+ ALL from a terminated Takeda sponsored Phase 1/2 study (Ponatinib-1501), including 11 enrolled participants.

Due to the differences in study design, study populations, and treatments administered, pooled analyses of safety data from INCB 84344 102 and Ponatinib-1501 were not performed.

Study INCB 84344-102

INCB 84344-102 is an ongoing, open-label, single-arm, Phase 1/2 study of ponatinib monotherapy in paediatric participants (ages ⩾ 1 to < 18 years) with recurrent or refractory leukemias or solid tumors and with a CP-CML expansion cohort.

The primary objective of Phase 1 of the study was to determine the MTD and/or RP2D of oral ponatinib administered QD in paediatric participants with selected advanced hematologic malignancies or solid tumors. The primary objectives of Phase 2 were to determine the efficacy of oral ponatinib administered QD in paediatric participants, and tThe secondary safety endpoints were frequency and severity of AEs and SAEs, Changes in vital signs and clinical evaluations, and Changes in clinical laboratory blood samples.

Participants in Phase 1 (dose escalation) and Phase 2 (dose expansion) were to be enrolled in 3 age cohorts (Cohort 1: ≥ 12 to < 18 years old; Cohort 2: ≥ 6 to < 12 years old; and Cohort 3: ≥ 1 to < 6 years old):

- Enrollment in the Phase 1 portion of the study comprised participants with advanced leukemias, lymphomas, and other paediatric tumors, including central nervous system tumors, and was completed for all 3 age cohorts.
- Enrollment in the Phase 2 portion of the study comprises participants with CP-CML (Group A) in addition to participants with other tumors, including selected advanced leukemias, lymphomas, and solid tumors (Group B). For participants in Group A, enrollment into age Cohorts 1 and 2 is ongoing; enrollment into Cohort 3 had not opened at the time of the data cutoff. For participants in Group B, enrollment into all age cohorts was completed.

5.4.1.1. Dose-Limiting Toxicities in Phase 1 and Recommended Phase 2 Dose

None of the 28 participants included in the DLT-Evaluable Analysis Set had any DLTs during the evaluation period. Upon review of the preliminary safety and PK data, and in agreement with the Data Safety Monitoring Board, the ponatinib RP2D was established as the weight equivalent of a 45-mg dose in adults.

Table 12: Study INCB 84344-102: Phase 1 and Phase 2 Ponatinib Doses

	Body Weight			
	≥ 45 kg	**≥ 30 kg to < 45 kg**	**≥ 15 kg to < 30 kg**	**≥ 5 kg to < 15 kg**
Phase 1 Cohort 1				
DL1	20 mg	15 mg	–	–
DL2	30 mg	20 mg	–	–
DL3	45 mg	30 mg	–	–
Phase 1 Cohorts 2 and 3 and Phase 2 Cohorts 1 and 2				
Recommended starting doses	45 mg	30 mg	15 mg	5 mg

Note: Cohort 1: participants ≥ 12 to 18 years old; Cohort 2: participants ≥ 6 to < 12 years old; Cohort 3: participants ≥ 1 to < 6 years old.
Source: INCB 84344-102 Protocol Section 6.1.

5.4.2. Patient exposure

Overall study population

In the overall study population, 37 participants were aged ≥ 12 to < 18 years (Cohort 1), 15 participants ≥ 6 to < 12 years (Cohort 2), and 9 participants ≥ 1 to < 6 years (Cohort 3).

Median age in the different treatment groups reflected the participant's age range for each cohort. Weight differed according to the participants' age range for each cohort; the median weight was 47.0 kg (range: 10.9, 80.0).

The median duration of exposure to ponatinib was 60 days (range:8-1742), with a median average daily dose of 30.0 mg (range: 5.0, 45.0) and a median total cumulative reported dose of 1380 mg, as of the cut-off date (25 Jan 2025) (Table 24).

Overall, as of the data cutoff date, 12 participants had dose increases or reductions during the study conduct. The most common reasons for study treatment discontinuation were disease progression (34 participants [55.7%]), AEs (5 participants [8.2%]), and death (3 participants [4.9%]), and the primary reason for withdrawing from study was death (34 participants [55.7%].

CP-CML Population

In the CP-CML population, the median age was 14.0 years (range: 7-17 years), corresponding with the majority of the participants (8 of 11) belonging to Cohort 1 (aged ≥ 12 to < 18 years). The three participants from Cohort 2 (aged ≥ 6 to < 12 years) were 7 (1 subject) and 11 (2 subjects) years old. The median body weight was 56.0 kg (range: 17.5, 72.0).

The median exposure to ponatinib was 559 days (range: 72-1100), the median average daily dose was 40.2 mg (range: 15.0, 45.0), and the median total cumulative dose was 22,815 mg. The median duration of ponatinib exposure for participants with CP-CML was substantially longer compared to that for participants with other leukemias and solid tumors (Table 24).

At the time of data cutoff date, all 11 CP-CML participants had received at least 1 dose of ponatinib treatment, 8 participants (72.7%) were still on treatment, and 3 participants (27.3%) had discontinued treatment. None of the participants had completed treatment

All participants were also still on study at the time of data cutoff date, and none had completed or withdrawn from study. Of the 3 participants who had discontinued treatment, 2 were due to AEs and 1 due to the investigator's decision.

Table 13: Study INCB 84344-102: Summary of Participant Disposition (Full Analysis Set With CP-CML)

Variable	Phase 1	Phase 2[a]		Total (N = 11)
	Cohort 2 DL1 (≥ 6 to < 12 y) (N = 1)	Cohort 1 (≥ 12 to < 18 y) (N = 8)	Cohort 2 (≥ 6 to < 12 y) (N = 2)	
Number (%) of participants treated	1 (100.0)	8 (100.0)	2 (100.0)	11 (100.0)
Number (%) of participants with ongoing treatment	1 (100.0)	5 (62.5)	2 (100.0)	8 (72.7)
Number (%) of participants who discontinued treatment	0 (0.0)	3 (37.5)	0 (0.0)	3 (27.3)
Primary reason				
AE	0 (0.0)	2 (25.0)	0 (0.0)	2 (18.2)
Physician decision	0 (0.0)	1 (12.5)	0 (0.0)	1 (9.1)
Number (%) of participants still in the study	1 (100.0)	8 (100.0)	2 (100.0)	11 (100.0)

Table 14 - Summary of Exposure to Ponatinib (Full Analysis Set)

Variable	Phase 1					Phase 2				Total (N = 61)
	Cohort 1 (≥ 12 to < 18 y)			Cohort 2 (≥ 6 to < 12 y)	Cohort 3 (≥ 1 to < 6 y)	Cohort 1 (≥ 12 to < 18 y)		Cohort 2 (≥ 6 to < 12 y)		
	DL 1 (N = 3)	DL 2 (N = 6)	DL 3 (N = 6)	DL 1 (N = 8)	DL 1 (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	611.7	43.5	57.8	168.1	43.6	568.9	140.4	441.0	47.6	193.7
STD	978.95	29.26	41.68	288.07	55.51	394.09	194.22	202.23	29.97	329.91
Min	36	22	27	14	17	72	8	298	18	8
Median	57.0	28.5	44.0	60.0	28.0	533.0	81.0	441.0	33.0	60.0
Max	1742	98	134	864	191	1100	765	584	86	1742
Average daily dose (mg)										
n	3	6	6	8	9	8	14	2	5	61
Mean	18.27	30.00	42.50	22.50	10.59	37.63	38.82	30.00	24.05	29.34
STD	2.837	0.000	6.124	8.018	5.228	10.351	9.101	21.213	13.500	13.400
Min	15.0	30.0	30.0	15.0	5.0	15.0	15.0	15.0	12.6	5.0
Median	19.82	30.00	45.00	22.50	15.00	40.59	45.00	30.00	17.67	30.00
Max	20.0	30.0	45.0	30.0	15.0	45.0	45.0	45.0	45.0	45.0

5.4.3. Adverse events

5.4.3.1. Overall Summary of the TEAEs

Overall population

Overall, 59 participants (96.7%) had at least 1 TEAE as of the IA data cutoff date.

Table 15 - Study INCB 84344-102: Overall Summary of Treatment-Emergent Adverse Events (Full Analysis Set)

	Phase 1					Phase 2				
	Cohort 1 (≥ 12 to < 18 y)			Cohort 2 (≥ 6 to < 12 y)	Cohort 3 (≥ 1 to < 6 y)	Cohort 1 (≥ 12 to < 18 y)		Cohort 2 (≥ 6 to < 12 y)		
Participants (n [%]) With:	DL 1 (N = 3)	DL 2 (N = 6)	DL 3 (N = 6)	DL 1 (N = 8)	DL 1 (N = 9)	CP-CML (N = 8)	Other Tumors (N = 14)	CP-CML (N = 2)	Other Tumors (N = 5)	Total (N = 61)
TEAE	3 (100.0)	6 (100.0)	5 (83.3)	8 (100.0)	9 (100.0)	8 (100.0)	14 (100.0)	1 (50.0)	5 (100.0)	59 (96.7)
TEAE related to ponatinib	2 (66.7)	3 (50.0)	3 (50.0)	7 (87.5)	7 (77.8)	6 (75.0)	14 (100.0)	1 (50.0)	4 (80.0)	47 (77.0)
Grade 3 or higher TEAE	2 (66.7)	1 (16.7)	2 (33.3)	3 (37.5)	4 (44.4)	4 (50.0)	9 (64.3)	0 (0.0)	5 (100.0)	30 (49.2)
Grade 3 or higher TEAE related to ponatinib	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	3 (37.5)	7 (50.0)	0 (0.0)	2 (40.0)	13 (21.3)
Fatal TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	2 (14.3)	0 (0.0)	0 (0.0)	3 (4.9)
Serious TEAE	1 (33.3)	3 (50.0)	1 (16.7)	3 (37.5)	4 (44.4)	2 (25.0)	7 (50.0)	0 (0.0)	4 (80.0)	25 (41.0)
Serious TEAE related to ponatinib	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	4 (28.6)	0 (0.0)	0 (0.0)	5 (8.2)
TEAE of special interest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	1 (1.6)
Dose reduction because of a TEAE	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (7.1)	0 (0.0)	1 (20.0)	4 (6.6)
Temporary interruption of study treatment because of a TEAE	1 (33.3)	0 (0.0)	2 (33.3)	2 (25.0)	1 (11.1)	3 (37.5)	7 (50.0)	0 (0.0)	3 (60.0)	19 (31.1)
Permanent discontinuation of study treatment because of a TEAE	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (11.1)	2 (25.0)	2 (14.3)	0 (0.0)	0 (0.0)	6 (9.8)
DLT during the DLT evaluation period (first 28 days of treatment)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note 1: A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first administration of study drug and within 30 days of the last dose of study drug.
Note 2: A treatment-related TEAE is a TEAE judged by the investigator as related to ponatinib treatment or with a missing causality.
Source: Table 3.2.1.

The most frequently reported TEAEs by SOC (> 40% of participants) were gastrointestinal disorders (34 participants [55.7%]), investigations (33 participants [54.1%]), skin and subcutaneous tissue disorders (32 participants [52.5%]), general disorders and administration site conditions (26 participants [42.6%]), and infections and infestations (25 participants [41.0%]). The most frequently reported TEAEs (> 15% of participants) by PT included pyrexia (21 participants [34.4%]), vomiting (15 participants [24.6%]), headache (13 participants [21.3%]), ALT increased and anemia (12 participants [19.7%] each), rash (11 participants [18.0%]), and constipation and nausea (10 participants [16.4%] each.

The most frequently reported drug-related TEAEs (> 20% of participants) were in the SOCs of skin and subcutaneous tissue disorders (23 participants [37.7%]), investigations (18 participants [29.5%]), gastrointestinal disorders (16 participants [26.2%]), and blood and lymphatic system disorders (14 participants [23.0%]; refer to INCB 84344-102 CSR Table 36). The most frequently reported ponatinib-related TEAEs (> 5% of participants) by PT included rash and vomiting (9 participants [14.8%] each), thrombocytopenia (8 participants [13.1%]), ALT increased (7 participants [11.5%]), GGT increased (6 participants [9.8%]), nausea and neutropenia (5 participants [8.2%] each), and anemia (4 participants [6.6%]).

Grade 3 or higher TEAEs, including fatal (Grade 5) events, were reported in 30 participants (49.2%). The most frequently occurring Grade 3 or higher TEAEs (> 5% of participants) by PT included neutropenia and ALT increased. Three participants (4.9%) had TEAEs with a fatal outcome (ascites,

COVID-19 pneumonia, tumor hemorrhage, and brain edema [the last 2 occurring in the same participant simultaneously]).

Participants With CP-CML

Table 16 - Study INCB 84344-102: Overall Summary of Treatment-Emergent Adverse Events (CP-CML)

Participants (n [%]) With:	**Total (N = 11)**
TEAE	10 (90.9)
TEAE related to ponatinib	8 (72.7)
Grade 3 or higher TEAE	4 (36.4)
Grade 3 or higher TEAE related to ponatinib	3 (27.3)
Fatal TEAE	0 (0.0)
Serious TEAE	3 (27.3)
Serious TEAE related to ponatinib	1 (9.1)
TEAE of special interest	0 (0.0)
Dose reductions because of a TEAE	1 (9.1)
Temporary interruption of study treatment because of a TEAE	4 (36.4)
Permanent discontinuation of study treatment because of a TEAE	2 (18.2)
DLT during the DLT-evaluation period (first 28 days of treatment)	0 (0.0)

Note 1: A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first administration of study drug and within 30 days of the last dose of study drug.
Note 2: A treatment-related TEAEs is a TEAE judged by the investigator as related to ponatinib treatment or with a missing causality.
Source: INCB 84344-102 CSR Table 32.

Table 17 - Summary of Treatment-Emergent Adverse Events Reported in ≥ 2 Participants by MedDRA System Organ Class and Preferred Term (Full Analysis Set With CP-CML)

MedDRA SOC PT	**Total (N = 11)**
Number (%) of participants with any TEAE	10 (90.9)
Infections and infestations	7 (63.6)
Influenza	2 (18.2)
Skin and subcutaneous tissue disorders	7 (63.6)
Erythema	2 (18.2)
Gastrointestinal disorders	5 (45.5)
Abdominal pain	2 (18.2)
Nausea	2 (18.2)
General disorders and administration site conditions	5 (45.5)
Pyrexia	5 (45.5)
Respiratory, thoracic and mediastinal disorders	4 (36.4)
Cough	2 (18.2)
Nervous system disorders	3 (27.3)
Headache	3 (27.3)

MedDRA SOC PT	Total (N = 11)
Blood and lymphatic system disorders	2 (18.2)
Neutropenia	2 (18.2)
Thrombocytopenia	2 (18.2)
Vascular disorders	2 (18.2)
Hypertension	2 (18.2)

Note 1: A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first administration of study drug and within 30 days of the last dose of study drug.
Note 2: Participants were counted once under each MedDRA SOC and PT.
Note 3: Adverse events were coded using MedDRA 27.1.
Source: INCB 84344-102 CSR Table 34.

Table 18 - Study INCB 84344-102: Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Full Analysis Set With CP-CML)

MedDRA SOC PT	Total (N = 11)
Number (%) of participants with any treatment-related TEAE	8 (72.7)
Skin and subcutaneous tissue disorders	4 (36.4)
Acne	1 (9.1)
Erythema	1 (9.1)
Pityriasis rubra pilaris	1 (9.1)
Rash	1 (9.1)
Investigations	3 (27.3)
Ejection fraction decreased	1 (9.1)
Lipase increased	1 (9.1)
Platelet count decreased	1 (9.1)
White blood cell count decreased	1 (9.1)
Blood and lymphatic system disorders	2 (18.2)
Neutropenia	2 (18.2)
Thrombocytopenia	2 (18.2)
Gastrointestinal disorders	2 (18.2)
Nausea	2 (18.2)
Abdominal pain	1 (9.1)
Vomiting	1 (9.1)
Cardiac disorders	1 (9.1)
Pericardial effusion	1 (9.1)
Congenital, familial and genetic disorders	1 (9.1)
Ichthyosis	1 (9.1)
Eye disorders	1 (9.1)
Dry eye	1 (9.1)
Hepatobiliary disorders	1 (9.1)
Hyperbilirubinaemia	1 (9.1)
Musculoskeletal and connective tissue disorders	1 (9.1)
Myalgia	1 (9.1)
Nervous system disorders	1 (9.1)
Headache	1 (9.1)

Note 1: A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first administration of study drug and within 30 days of the last dose of study drug.
Note 2: A treatment-related TEAE is a TEAE judged as related to ponatinib by the investigator or with a missing causality.

Note 3: Participants were counted once under each MedDRA SOC and PT.
Note 4: Adverse events were coded using MedDRA 27.1.
Source: INCB 84344-102 CSR Table 37.

Grade 3 or higher TEAEs were reported in 4 participants (36.4%) with CP-CML and included TEAEs by PT of ALT increased, neutropenia, ejection fraction decreased, lipase increased, and platelet count decreased (1 participant [9.1%] each). No Grade 5 TEAEs were reported.

5.4.3.2. Adverse drug reactions

Adverse reactions were identified based on results from 61 paediatric participants with R/R leukemias or solid tumors in Study INCB 84344-102 who received ponatinib monotherapy.

The adverse reactions identified for ponatinib monotherapy in paediatric participants and included in the SmPC are based on the sponsor's medical assessment of each individual TEAEs where a causal relationship with the treatment is a reasonable possibility. The review consisted of all TEAEs from the FAS, including TEAEs ≥ Grade 3, serious TEAEs, fatal TEAEs, and TEAEs leading to discontinuation of study drug. The following factors were considered when making decisions:

- Frequency of reporting
- Severity
- TEAE observed with ponatinib in paediatrics versus adults
- TEAE known to be caused by related drug
- TEAEs leading to a higher rate of treatment discontinuation than expected
- Any clinically significant laboratory values recorded as TEAEs and identified or potential risks were considered
- Biological/pharmacological plausibility based on ponatinib's mechanism of action and known effects of BCR-ABL TKIs
- Timing of the event relative to the time of ponatinib exposure
- Population under study

Table 30 - Study INCB 84344-102: Adverse Reactions Observed in Paediatric Participants – Frequency Reported by Incidence of Treatment-Emergent Events

System Organ Class	Frequency	Ponatinib Monotherapy (N = 61)
Infections and infestations	Common	Pneumonia (3.3%), respiratory tract infection (3.3%), conjunctivitis (1.6%), folliculitis (1.6%), rash pustular (1.6%), sepsis (1.6%), upper respiratory tract infection (1.6%)
Blood and lymphatic system disorders	Very common	Anaemia (19.7%), thrombocytopenia (13.1%), neutropenia (11.5%)
	Common	Platelet count decreased (9.8%), lymphopenia (4.9%), white blood cell count decreased (4.9%), leukopenia (3.3%), neutrophil count increased (3.3%), eosinophilia (3.3%), febrile neutropenia (1.6%)
Endocrine disorders	Common	Hypothyroidism (3.3%)

System Organ Class	Frequency	Ponatinib Monotherapy (N = 61)
Metabolism and nutrition disorders	Common	Decreased appetite (3.3%), hypertriglyceridaemia (4.9%), hypophosphataemia (4.9%), hyperuricemia (3.3%), hypocalcaemia (3.3%), hyperamylasaemia (1.6%), hyperlipasaemia (1.6%), hypoalbuminaemia (1.6%), hypokalaemia (1.6%), weight decreased (1.6%)
Psychiatric disorders	Common	Insomnia (1.6%)
Nervous system disorders	Very common	Headache (21.3%)
	Common	Dizziness (1.6%), hyperaesthesia (1.6%), migraine (1.6%), paraesthesia (1.6%)
Eye disorders	Common	Dry eye (4.9%), eyelid oedema (3.3%), ocular hyperaemia (1.6%), blepharitis (1.6%), eye pain (1.6%), periorbital oedema (1.6%), vision blurred (1.6%)
Cardiac disorders	Common	Ejection fraction decreased (6.6%), pericardial effusion (3.3%), bradycardia (1.6%), palpitations (1.6%), tachycardia (1.6%)
Vascular disorders	Common	Hypertension (9.8%), flushing (1.6%), hot flush (1.6%)
Respiratory, thoracic and mediastinal disorders	Common	Cough (6.6%), pleural effusion (3.3%), dysphonia (1.6%)
Gastrointestinal disorders	Very common	Vomiting (24.6%), constipation (16.4%), nausea (16.4%), abdominal pain (11.5%)
	Common	Diarrhoea (9.8%), lipase increased (4.9%), amylase increased (1.6%), gastritis (1.6%), stomatitis (1.6%), oropharyngeal pain (1.6%), lipase (1.6%)
Hepatobiliary disorders	Very common	Alanine aminotransferase increased (19.7%), gammaglutamyltransferase increased (14.8%), aspartate aminotransferase increased (11.5%)
	Common	Blood alkaline phosphatase increased (3.3%), hyperbilirubinaemia (1.6%), hypertransaminasaemia (1.6%)
Skin and subcutaneous tissue disorders	Very common	Rash (18.0%)
	Common	Erythema (8.2%), dry skin (6.6%), acne (3.3%), dermatitis acneiform (3.3%), eczema (3.3%), pruritus (3.3%), rash erythematous (1.6%), rash macular (3.3%), rash maculo-papular (3.3%), alopecia (1.6%), keratosis pilaris (3.3%), pain of skin (1.6%), pityriasis rubra pilaris (1.6%), contusion (1.6%)
Musculoskeletal and connective tissue disorders	Very common	Back pain (14.8%), arthralgia (11.5%)
	Common	Pain in extremity (9.8%), myalgia (4.9%), musculoskeletal chest pain (3.3%), musculoskeletal pain (3.3%), bone pain (3.3%), neck pain (1.6%)
Reproductive system and breast disorders	Common	Amenorrhoea (1.6%)
General disorders and administration site conditions	Very common	Pyrexia (34.4%)
	Common	Fatigue (8.2%), asthenia (3.3%), influenza like illness (1.6%), noncardiac chest pain (3.3%), oedema peripheral (4.9%)
Renal and urinary disorders	Common	Proteinuria (6.6%)
Investigations	Common	Creactive protein increased (3.3%)

Note: SOC categorization follows the ICLUSIG SmPC (2025).
Source: INCB 84344-102 CSR Table 3.2.2.

5.4.4. AEs of special interest, serious adverse events and deaths, other significant events

5.4.4.1. Treatment-Emergent Adverse Events of Special Interest and Other Adverse Events of Significance

Arterial occlusive events (AOE) and VTEs have been identified as AESIs for ponatinib in adult participants.

In the overall population, 1 participant (1.6%) had an event of noncardiac chest pain that met the Protocol-defined criteria for AOEs. The participant was from Phase 2 and had metastatic Ewing sarcoma. The event was Grade 2 in severity, serious, and was assessed by the investigator as not related to ponatinib treatment. The event led to treatment interruption and resolved 3 days after onset. No VTEs were reported.

No AESIs (AOEs or VTEs as defined per Protocol) were reported **in participants with CP-CML.**

5.4.4.2. Other Serious Treatment-Emergent Adverse Events

In the overall population, serious TEAEs were reported in 25 participants (41.0%). The most frequently reported (> 5% of participants) by SOC were general disorders and administration site conditions (8 participants [13.1%]), nervous system disorders (7 participants [11.5%]), infections and infestations (5 participants [8.2%]), and gastrointestinal disorders (4 participants [6.6%]).

The most frequently reported serious TEAEs (≥ 2 participants) by PT were pyrexia (7 participants [11.5%]), seizure (5 participants [8.2%]), ejection fraction decreased (3 participants [4.9%]; see Section 4.1.2), and back pain (2 participants [3.3%]).

In the CP-CML population there were 3 participants (27.3%) who had serious TEAEs: 2 participants (18.2%) with events of pyrexia and 1 participant (9.1%) with an event of ejection fraction decreased. All of these serious TEAEs resolved. The events of pyrexia were assessed as not related to ponatinib, whereas the ejection fraction decreased event was assessed as related to ponatinib and treatment was discontinued.

5.4.4.3. Deaths

In the **overall population**, three study participants (4.9%) had TEAEs with a fatal outcome. The fatal events were ascites, COVID-19 pneumonia, and tumor hemorrhage and brain edema (the last 2 occurring in the same participant simultaneously). None were assessed by the investigators to be related to ponatinib treatment. The events of ascites, tumor hemorrhage, and brain edema were assessed as related to the underlying disease. In detail:

• A 4-year-old female participant from Phase 1 Cohort 3 (DL 1) with a metastatic extracranial tumor had a fatal event of ascites on Day 22, which was assessed by the investigator as not related to ponatinib and related to the underlying "study disease."

• A 15-year-old female participant from Phase 2 Cohort 1 with an advanced CNS neoplasm had a fatal event of COVID-19 pneumonia on Day 86. The event was assessed by the investigator as not related to ponatinib treatment.

• A 14-year-old female participant from Phase 2 Cohort 1 with an advanced CNS neoplasm had 2 fatal events concurrently (tumor hemorrhage and brain edema) that started on Day 197 and ended on Day

198. Both events were assessed by the investigator as not related to ponatinib and related to the underlying medical condition.

No fatal TEAEs were reported in the **CP-CML group.**

5.4.5. Discontinuation due to adverse events

5.4.5.1. Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug

Overall, 6 participants (9.8%) had TEAEs leading to permanent discontinuation of ponatinib treatment. The events were ALL, ascites, COVID-19 pneumonia, ejection fraction decreased, platelet count decreased, and pleural effusion (all in 1 participant [1.6%] each). The event of ALL was reported in a participant who was initially misdiagnosed with Ewing sarcoma and was determined to have lymphoblastic leukemia upon further investigation. The participant was withdrawn from treatment and the study.

The event of ejection fraction decreased that led to treatment discontinuation was in a participant with CP-CML from Phase 2 Cohort 1. The event was assessed by the investigator as related to ponatinib treatment and resolved.

5.4.5.2. Treatment-Emergent Adverse Events Leading to Dose Reduction of Study Drug

Overall, 4 participants (6.6%) had TEAEs that led to dose reductions, including 1 participant (9.1%) with CP-CML, 2 participants with solids tumors, and 1 participant with ALL. None of the events were serious and all resolved.

One participant from Phase 2 Cohort 1 with CP-CML had a TEAE of lipase increased that was Grade 3 in severity, not serious, and reported by the investigator as related to ponatinib treatment. The ponatinib dose was reduced from 45 to 30 mg.

5.4.6. Safety in special populations

5.4.6.1. Intrinsic Factors

In both Phase 1 and Phase 2 portions of Study INCB 84344-102, participants are to be enrolled in 3 cohorts: Cohort 1 (aged ≥ 12 to < 18 years), Cohort 2 (aged ≥ 6 to < 12 years), and Cohort 3 (aged ≥ 1 to < 6 years). Phase 1 enrollment is complete, and Phase 2 enrollment is ongoing.

Overall, in Phases 1 and 2, there were no discernable differences in the incidences of TEAEs, treatment-related TEAEs, or serious TEAEs by age group (Table 25). Additionally, there were no notable differences in the types of TEAEs reported by age group.

5.4.6.2. Extrinsic Factors

The impact of extrinsic factors was not evaluated in Study INCB 84344-102 due to the small sample size.

5.4.6.3. Drug Interactions

No drug-drug interaction data are available for this application.

5.4.6.4. Use in Pregnancy and Lactation

No pregnancies were reported in either study. Refer to the currently approved SmPC.

5.4.6.5. Overdose

No overdoses were reported in Study INCB 8344-102 at the time of data cut off or in Study Ponatinib-1501.

5.4.6.6. Drug Abuse

Ponatinib has no known abuse potential based on its chemical and pharmacologic properties and mechanism of action.

5.4.6.7. Withdrawal and Rebound

Studies to examine withdrawal and rebound are not relevant for drugs in ponatinib's class. The drug is often withdrawn for progressive disease or for AEs; no adverse effects are expected from the withdrawal itself.

5.4.6.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

The effect of ponatinib on the ability to drive or operate machinery or mental ability was not specifically measured.

5.4.6.9. Exposure-Response Safety Analyses

In Study INCB 84344-102, post hoc analyses were performed to assess the relationship between ponatinib steady-state exposure (AUC0-24h) in participants with or without Grade 3 or higher TEAEs. Results indicated no difference in exposures for participants with a Grade 3 or higher TEAE compared to exposures in participants without these TEAEs. There were 2 participants who had TEAEs of Grade 3 or higher thrombocytopenia assessed by the investigator as related to ponatinib treatment. The steady-state exposure in these 2 participants was within the range of exposures observed in participants who did not experience this TEAE.

5.4.6.10. Safety Results in the Paediatric and Adult CP-CML Populations

The safety outcomes in the paediatric CP-CML population (aged ≥ 6 to < 18 years) from Study INCB 84344-102 are descriptively compared with those previously established in adults for the same indication from the 45-mg cohort (N = 94) of the Phase 2 OPTIC study at the time of 5-year follow-up in support of the extrapolation of the safety profile. The median ponatinib exposure for the CP-CML population in the paediatric study was 559 days. At the time of the 5-year follow-up analysis of the OPTIC study, the median ponatinib exposure for the 45-mg cohort was longer (927.5 days) and the daily dose intensity was lower (27.7 mg). In this cohort, 45 of the 56 participants (80.4%) who had an MR had their doses reduced to 15 mg.

The most frequently reported (> 2 participants) serious TEAEs in the 45-mg cohort in the OPTIC study were thrombocytopenia (5 participants [5.3%]), pyrexia (4 participants [4.3%]), and anemia (3 participants [3.2%]), whereas in the CP-CML population in the paediatric study was pyrexia (2 participants [18.2%]) and decreased ejection fraction (1 participant [9.1%]). In the 45-mg cohort in

the OPTIC study, 4 Grade 5 events were reported, while 13 participants (13.8%) had AOEs and 1 participant had a VTE. Five participants (5.3%) had AOEs that led to treatment discontinuation. No fatal events or AESIs were reported in the paediatric CP-CML population.

5.4.7. Immunological events

N/A

5.4.8. Safety related to drug-drug interactions and other interactions

N/A

5.4.9. Vital signs and laboratory findings

5.4.9.1. Haematology

Fluctuations in the haematology parameters at baseline and during the study treatment were observed. There were decreases from baseline in the mean values for haemoglobin, leukocytes, and lymphocytes, and increases from baseline in the mean values for haemoglobin, neutrophils, leukocytes, and platelets. The mean values for leukocytes initially decreased during the study and then variably showed increases and decreases from baseline. Mean values for some of the hematology parameters also increased or decreased during the first cycles of treatment but tended to normalize/recover.

The number of participants who had shifts in hematology values was low, with mostly single participants having shifts of laboratory values by $\geq$ 2 grades. There were few participants who had a worst grade hematology values of Grade 3 or 4. The following worsening from baseline to NCI CTCAE Grade 3 or Grade 4 abnormalities on study were observed:

• Increased haemoglobin worsened from baseline (not graded) to Grade 3 post baseline in 2 participants.

• Decreased leukocytes (leukopenia) worsened from Grade 0 (normal) at baseline to Grade 3 postbaseline in 1 participant, from Grade 1 to Grade 3 in 1 participant, and from Grade 2 to Grade 3 in 1 participant.

• Increased lymphocytes (lymphocytosis) worsened from Grade 0 at baseline to Grade 3 postbaseline in 1 participant.

• Decreased lymphocytes (lymphopenia) worsened from Grade 1 at baseline to Grade 3 postbaseline in 3 participants, Grade 2 to Grade 3 in 2 participants.

• Decreased neutrophils (neutropenia) worsened from Grade 0 at baseline to Grade 4 postbaseline in 3 participants, from Grade 0 to Grade 3 in 4 participants.

• Decreased platelets (thrombocytopenia) worsened from Grade 0 at baseline to Grade 3 postbaseline in 3 participants and Grade 1 to Grade 3 in 2 participants.

Participants With CP-CML

Mean hematology parameters values at baseline were normal for the majority of participants except leukocytes that were increased or decreased in some participants. Neutrophil levels decreased at the beginning of the treatment in a few participants, but levels returned to normal. Participants with shifts

in hematology values were low, with mostly single participants having shifts of laboratory values by ≥ 2 grades. One participant in Phase 1 had neutrophil levels worsen from Grade 0 at baseline to Grade 4 postbaseline, and 1 participant in Phase 2 had neutrophil levels worsen from Grade 0 to Grade 3. One participant in Phase 2 had decreased platelet counts worsen from Grade 0 to Grade 3.

In participants with CP-CML, in the SOC blood and lymphatic system disorders TEAEs of neutropenia and thrombocytopenia were reported in 2 participants each. In the SOC investigations, platelet count decreased and white blood cell count decreased were reported in 1 participant each.

5.4.9.2. Chemistry

Baseline chemistry values were generally normal for the majority of participants. The mean values for ALT, AST, GGT, and lipase increased from baseline during the study, and results were outside the normal range for some participants.

The number of participants who had shifts in chemistry values was low, with mostly single participants having shifts of laboratory values by ≥ 2 grades. There were few participants who had a worst hematology value of Grade 3 or 4. The following worsening from baseline to NCI CTCAE Grade 3 or 4 abnormalities on study were observed:

• Increased ALT worsened from baseline (not graded) to Grade 3 postbaseline in 5 participants.

• Increased AST worsened from baseline (not graded) Grade 3 postbaseline in 1 participant.

• Decreased derived calcium corrected for albumin worsened from Grade 0 at baseline to Grade 4 postbaseline in 1 participant.

• Increased GGT worsened from baseline (missing) to Grade 3 postbaseline in 1 participant.

• Glucose levels worsened from Grade 0 at baseline to Grade 3 postbaseline in 1 participant, and from Grade 0 to Grade 4 in 1 participant.

• Increased lipase worsened from Grade 0 at baseline to Grade 3 postbaseline in 1 participant, and from Grade 2 to Grade 3 in 1 participant.

• Increased potassium worsened from Gade 0 at baseline to Grade 3 postbaseline in 1 participant.

In participants with CP-CML, mean values at baseline were high for albumin, ALT, AST, and bilirubin for some participants. Two participants had shifts in ALT increased worsening from baseline (not graded) to Grade 3 postbaseline, and 1 participant had decreased derived calcium corrected for albumin that worsened from Grade 0 at baseline to Grade 4 postbaseline. ALT increased, AST increased, blood alkaline phosphatase increased, hyperbilirubinemia, lipase increased, and hyperuricemia were reported in 1 participant each.

5.4.9.3. Vital Signs

Most participants had normal vital signs measurements at baseline and at all timepoints assessed. Changes were generally small, and no clinically meaningful trends were observed.

The majority of participants had low diastolic and systolic blood pressure at baseline and during treatment (especially the first cycles of treatment) in both the overall CP-CML populations. Pulse and respiratory rate showed some variability (mostly increases), which did not raise any concern, possibly attributed to initial anxiety during study visits. In the overall population, 6 participants (9.8%) had a TEAE of hypertension, all 6 from the older age group (Cohort 1: ≥ 12 to < 18 years).

The majority if participants had low diastolic and systolic blood pressure at baseline and during treatment (especially the first cycles of treatment) in both the overall and CP-CML populations. Pulse and respiratory rate showed some variability (mostly increases), which did not raise any concern, possibly attributed to initial anxiety during study visits.

5.4.9.4. Electrocardiograms and Cardiac Findings

QT intervals were generally normal for most study participants but were decreased for a few participants in the younger age group.

Two participants in Phase 2 Cohort 1, both with solid tumors, had serious TEAEs of ejection fraction decreased. One of the TEAEs resulted in treatment interruption. These TEAEs were not resolved at the time of IA data cutoff and were considered related to ponatinib.

One participant with a solid tumor in Phase 1 Cohort 2, DL1, had a nonserious TEAE of ejection fraction decreased that was considered not related to ponatinib and was ongoing at the time of IA data cutoff.

One participant with CP-CML in Phase 2 Cohort 1 had a serious TEAE of ejection fraction decreased resulting in treatment discontinuation. The TEAE was considered related to ponatinib and had resolved.

5.4.10. Post marketing experience

No long-term use or postmarketing experience is available for paediatric patients.

Up to 13 Dec 2024, the estimated worldwide cumulative postmarketing exposure to ponatinib since 14 Dec 2012 (International Birth Date) was approximately 44,893 PYs (data on file). This estimate assumes an average daily dose of 30 mg based on the current product labeling. The highest cumulative exposure is among patients treated in the European Economic Area, UK, and Switzerland (17,500 PYs) and the US and Canada (13,422 PYs). Because the postmarketing exposure is based on sales/shipment data, it is not possible to present the exposure by gender, age, dose, dosage form, or other factors. In addition, no noninterventional studies (including registries) investigating postapproval use have been conducted in special populations.

As of 13 Dec 2024, a total of 19,382 serious adverse drug reactions were reported in the 12,771 postmarketing cases received for ponatinib. Most serious adverse drug reactions were reported from noninterventional studies and reports from other solicited sources.

Ponatinib is not approved for use in the paediatric population. Off-label ponatinib use cases are reviewed as part of the routine pharmacovigilance activities. The review of the off-label use cases, including cases where ponatinib is administered to patients outside the indicated age population, has not revealed any new safety information outside the current safety profile for the approved indications.

5.4.11. Overall discussion and conclusions on clinical safety

5.4.11.1. Discussion

The safety assessment in the applied paediatric indication is based on data from the INCB 84344-102 study, an ongoing, open-label, single-arm, Phase 1/2 study of ponatinib monotherapy in paediatric participants (ages ≥ 1 to < 18 years) with recurrent or refractory leukemias or solid tumors and with a CP-CML expansion cohort.

As of the data cutoff date (25 Jan 2025), the study had enrolled 61 participants who received at least 1 dose of ponatinib (Overall population, FAS), of whom 11 participants comprised CP-CML FAS subset.

The median age of all participants was 13 years (range: 1-17). In participants with CP-CML (Phase 1 [1 participant] and Phase 2 [10 participants]), the median age was 14.0 years, corresponding with the majority of the participants (8 of 11) belonging to Cohort 1 (≥ 12 and < 18 years of age).

Exposure

The median duration of treatment was 60 days (range: 0.20, 60.85) and the median average daily dose 30.0 mg (range: 5.0, 45.0) for the overall population, while the CP-CML population had a substantially longer median duration of treatment of 559 days (range: 72-1100), and a higher median average daily dose of 40.2 mg, (range: 15.0, 45.0).

Considering the long-term treatment required in CP-CML patients, the exposure in the non-CP-CML population is relatively short, while the CP-CML subset is limited in size. However, as the safety profile of ponatinib in adults is generally well characterised, the available experience is considered sufficient to support extrapolation of safety to the paediatric target population, given similar drug exposure.

It should be noted that the safety data presented are derived from exposures at doses lower than those proposed in the product information and should be interpreted with caution.

Adverse events/TEAEs

Almost all participants (96.7%) in the overall population and 10 participants (90.9%) in the CP-CML subset were reported to have at least 1 TEAE.

The most frequently reported TEAEs (> 15% of participants) by PT in the overall population included pyrexia (34.4%), vomiting (24.6%), headache (21.3%), anemia and ALT increased (19.7% each), rash (18.0%), and constipation and nausea (16.4% each).

The most frequently reported TEAEs in the CP-CML population (≥ 2 participants) were pyrexia (5 participants [45.5%]), headache (3 participants [23.7%]), and thrombocytopenia, neutropenia, nausea, influenza, hypertension, erythema, cough, and abdominal pain (2 participants [18.2%] each).

Grade ≥3 TEAEs were reported for 41.0% of participants in the overall population and in 4 participants (36.4%) in the CP-CML group, included TEAEs of ALT increased, neutropenia, ejection fraction decreased, lipase increased, and platelet count decreased.

The overall AE profile does not appear to differ substantially depending on age; however, no firm conclusions can be made due to the small sample size of the cohorts.

SAEs

Serious TEAEs were reported in 25 participants (41.0%) in the overall population and 3 (27.3%) in the CP-CML cohort. Pyrexia and ejection fraction decreased was among the most frequently reported in both cohorts.

TEAEs leading to death

TEAEs leading to death were observed in 3 participants (4.9%) (ascites, COVID-19 pneumonia, tumor hemorrhage, and brain edema), assessed as related to the underlying disease. No TEAEs with a fatal outcome were reported in the CP-CML population

TEAEs leading to dose reduction, interruption and treatment discontinuation

TEAEs leading to permanent discontinuation of ponatinib were reported in 6 participants (9.8%), of whom one with CP-CML due to ejection fraction decreased. Overall, 4 participants (6.6%) had TEAEs

that led to dose reductions, including 1 participant (9.1%) with CP-CML who had a not serious Grade 3 TEAE of lipase increased.

AESIs

Arterial occlusive events

One participant (1.6%) had an event of noncardiac chest pain that met the Protocol-defined criteria for AOEs. No participant with CP-CML reported an AOE.

VTEs

No VTEs were reported.

Clinical Laboratory Evaluations

Regarding haematology testing, few participants had shifts in hematology values, with mostly single participants having shifts of laboratory values by ≥ 2 grades. There were few participants who had a worst grade hematology values of Grade 3 or 4.

Baseline chemistry values were generally normal for the majority of participants. The mean values for ALT, AST, GGT, and lipase increased from baseline during the study, and results were outside the normal range for some participants. In the CP-CML population, two participants had shifts in ALT increased worsening from baseline (not graded) to Grade 3 postbaseline, and 1 participant had decreased derived calcium corrected for albumin that worsened from Grade 0 at baseline to Grade 4 postbaseline. No Hy's law cases are described. The risk of hepatotoxicity is decribed in the SmPC.

Adverse Drug Reactions (ADR)s

Adverse reactions were identified based on results from 61 paediatric participants with R/R leukaemias or solid tumors in Study INCB 84344-102 who received ponatinib monotherapy. The type and frequency of ADRs are generally in line with those reported in the adult population. The proposed new PT terms for inclusion in the SmPC section 4.8. ADR table are blepharitis, ocular hyperaemia, bradycardia, palpitations, tachycardia, acne, dermatitis acneiform, keratosis pilaris, contusion, pityriasis rubra pilaris, rash pustular, amenorrhoea, proteinuria, and hypoalbuminaemia.

Overall, ADRs are considered adequately described in 4.4. and 4.8 sections of the SmPC.

5.4.11.1.1. Overall assessment of available safety data

In Study INCB 84344-102 treatment-emergent AEs were reported in 96.7% of patients in the overall study population. The most common TEAEs were pyrexia, vomiting, headache, ALT increased and anemia and rash. A total of 41% of patients had serious TEAEs, with the most frequent by PT beingpyrexia, seizure, ejection fraction decreased and back pain. There were 3 participants (4.9%) with TEAEs with a fatal outcome, none assessed by the investigator as ponatinib-related (ascites, COVID-19 pneumonia, tumor hemorrhage and brain edema). In patients with CP-CML, treatment-emergent AEs were reported in 90.9% of participants (pyrexia, headache, thrombocytopenia, neutropenia, nausea, influenza, hypertension, erythema, cough, and abdominal pain). Serious TEAEs were reported in 3 (27.3%) participants (pyrexia & ejection fraction decreased). No fatal TEAEs were reported.

The data review from Study INCB 84344-102 did not reveal any new safety concerns in paediatric patients. The events observed were consistent with those previously identified in adult populations. The data from the overall study population (N=61) supports the limited data in the CP-CML group.

However, substantial differences in disease background, exposure duration, and dosing among the CP-CML patients and the overall population should be considered, as they complicate meaningful comparisons.

Focusing on the CP-CML cohort, no grade 5 events or AESIs (i.e., VOD and AOL) were reported in the CP-CML population. Overall, the identified risks are considered manageable and appropriately communicated in the product information. However, the safety data are derived from exposures at doses lower than those proposed in the product information and should be interpreted with caution.

The safety database is very limited, specifically in children between 6 and 12 years old, as well as children with lower body weight. Thus, conclusions on the clinical safety of ponatinib in paediatric use depend on a PK bridge to the safety database in adult.

5.4.11.1.2. Adverse drug reactions in the SmPC

The SmPC section 4.8 was updated with the ADRs based on results from 61 paediatric participants with R/R leukemias or solid tumors in Study INCB 84344-102 who received ponatinib monotherapy.

The ADRs proposed by the MAH for inclusion in the SmPC are described in section 5.4.3.2 above.

5.4.11.2. Conclusions on clinical safety

The safety profile of ponatinib in the paediatric population is generally in line with the safety profile observed in adults. No unexpected adverse reactions were identified. Of note, the safety database is limited and the safety assessment was supported by a PK bridge to the adult safety database.

6. Risk management plan

The MAH has submitted a new version of RMP (version 25.0) with final sign-off date 17/03/2026, which replaced the initially submitted RMP (version 23.4, final sign-off date 29/08/2025). The RMP has been updated to reflect the changes related to the new extension of the chronic myeloid leukaemia (CML) indication to paediatric patients 6 years of age or older with chronic phase-CML (CP-CML), and include Growth retardation as a new important potential risk. The (main) proposed changens concern Part I – Product Overview, Part II – Modules SI-SVIII, Part V – V.1 and Part VI, as per the proposed indication and Product Information.

The latest approved version of the RMP was 24.1 on 29 March 2026, following procedure EMA/VR/0000263550. No other RMP versions are currently under evaluation.

6.1. Safety specification

6.1.1. Proposed safety specification

The MAH has proposed the following changes of the Safety Specification:

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	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 add data on paediatric patients
Module SV	
SV.1	The section is updated to add the post-authorization exposure and total number of countries where ponatinib is approved as per a DLP of 13DEC2024
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 13DEC2024 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

Summary of the safety concerns

The MAH proposed the following summary of safety concerns in the RMP:

Table 19: 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

6.1.2. Discussion on proposed safety specification

No new safety concerns are identified following the review of safety data in the current procedure. It is noted that, according to the MAH, ponatinib may be associated with growth retardation in paediatric patients; growth outcomes in Study INCB 84344-102 have not been fully evaluated and will be assessed at the final analysis, which is endorsed. However, given the plausible mechanism and the suspected association of TKIs with growth retardation, the MAH proposed listing Growth Retardation as an important potential risk in the RMP, along with a warning in section 4.4 of the SmPC and section 2 of the package leaflet. The proposed updates are supported. No additional risk minimization measures or pharmacovigilance activities are considered necessary.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

In the submitted RMP version 25.0, the MAH considers that routine pharmacovigilance activities are considered sufficient to monitor the safety profile of the product and does not propose any changes to the routine and additional pharmacovigilance activities.

6.2.2. Discussion on the Pharmacovigilance Plan

6.2.2.1. Routine pharmacovigilance activities

The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product, and may be sufficient to monitor the effectiveness of the risk minimisation measures.

6.2.2.2. Additional pharmacovigilance activities

There are currently no planned additional pharmacovigilance activities.

6.3. Plans for post-authorisation efficacy studies

Table 32: 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 which 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	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	Long term efficacy	Final report	DEC 2028

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Reduced- Intensity Chemotherapy, in Patients With Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL)	MRD-negative CR rate at the end of induction The key secondary objective was to compare EFS between the 2 cohorts.			

In the current application, the MAH has not proposed any changes to the ongoing post-authorisation efficacy studies. This is acknowledged.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

The MAH did not propose any additional risk minimisation measures. The vascular occlusive events routine risk minimization activities text has been updated as per the proposed Product Information.

Table 33. Part V.1: Planned routine risk minimisation measures

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

Safety concern	Routine risk minimisation activities
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
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

Safety concern	Routine risk minimisation activities
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**

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

Routine risk minimisation measures are considered sufficient to minimise the risks of the product in the proposed indication(s).

6.4.2.2. Additional risk minimisation measures

The PRAC having considered the data submitted is of the opinion that no additional risk minimisation measures are required.

6.5. RMP Summary and RMP Annexes overall conclusion

The RMP Part VI and the RMP Annexes have been updated to reflect the changes related to the new extension of the CML indication to paediatric patients 6 years of age or older with CP-CML. The changes are considered acceptable.

6.6. PRAC Outcome

PRAC endorsed the PRAC Rapporteur's assessment of the RMP and its conclusions, without further additions.

6.7. Overall conclusion on the Risk Management Plan

☒ The CHMP and PRAC consider that the updated risk management plan version 25.0 is acceptable.

The MAH is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations

should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

See attached edited product information including agreed changes.

8.2. Labelling

See attached edited product information including agreed changes.

8.2.1. Package leaflet (PL)

See attached edited product information including agreed changes.

8.2.2. User consultation

8.2.2.1. Conclusion from the checklist for the review of user consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Iclusig film coated tablet. The bridging report submitted by the MAH has been found acceptable.

9. Benefit-risk assessment

9.1. Therapeutic context

9.1.1. Disease or condition, proposed therapeutic indication

Treatment of paediatric patients 6 years of age or older with chronic phase chronic myeloid leukaemia (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.

9.1.2. Available therapies and unmet medical need

For a detailed description, please see section 2 of this document.

The introduction of treatment with imatinib, a first-generation TKI, dramatically improved the prognosis of children and adolescents with CML (Leoni and Biondi 2015, Suttorp et al 2011); nonetheless, the initial presence or the development of resistance to imatinib due to mutations in the kinase domain is a common cause of disease recurrence (Leoni and Biondi 2015, Miller et al 2014).

Second-generation BCR ABL inhibitors including dasatinib, nilotinib and bosutinib are more potent inhibitors of native BCR ABL than imatinib and inhibit many, although not all, imatinib resistant BCR-ABL mutants (Cortes et al 2011, O'Hare et al 2007).

However, dasatinib, nilotinib, and bosutinib are ineffective against the T315I BCR ABL mutant (Soverini et al 2014), which is present in 11% to 20% of adult patients resistant to imatinib (Cortes et al 2011, O'Hare et al 2007). There still are limited approved therapeutic options for CML patients who are resistant or intolerant to second-generation TKI therapy or carry the T315I mutation.

9.2. Main clinical studies

Study INCB 84344-102 is an ongoing phase I/II, single-arm, open-label study to determine the safety and efficacy of ponatinib in paediatric patients with recurrent or refractory leukemias or solid tumors. The study consists of 2 parts.

- Phase 1 (completed) was run-in phase for dose finding of the MTD/RP2D of ponatinib monotherapy in paediatric participants (CML; N=1). PK was listed as the primary objective in this part of the study.

- Phase 2 (ongoing) followed a standard, single-arm, Phase 2 design and group A included paediatric participants with CP-CML who are resistant to or intolerant of at least 1 prior BCR-ABL–targeted TKI therapy or who have the kinase domain mutation T315I (CML; N=10). Participants received ponatinib as monotherapy. The primary objective for Phase 2 group A was to assess efficacy in this patient population.

The PK analyses included data from 55 paediatric study participants in Study INCB 84344-102 which included CML patients and other patient populations. Since there are limited PK data available in the target population (N=10 CML patients), paediatric PK data from patients with other diseases were used to support inferences on ponatinib PK in the target population.

The PK data was collected using sparse sampling and was analysed using PopPK modelling. The final model was used to perform PopPK-based simulations to support the proposed posology, including starting doses and reduced doses. The PopPK simulations included the steady-state PK exposure metrics AUC, Cmax and Ctrough.

The benefit-risk for the presently sought extension of indication is determined by extrapolation of efficacy and safety from the adult patient population by means of PK exposure matching. Thus, the PK data collected in INCB 84344-102 is considered pivotal for determining the benefit-risk balance of ponatinib in paediatric patients.

9.3. Favourable effects

According to simulations from the final PopPK model, the PK exposures for the proposed doses were comparable between paediatric patients and adults (see section 5.2.2.2.1.).

The primary endpoint for Phase 2, major cytogenetic response (MCyR) rate by 12 months (defined as complete cytogenetic response or partial cytogenetic response) was achieved by 90% (9 out of 10 participants [95% CI: 55.50, 99.75]), meaning that 90% had responded at some point before or up to 12 months. All participants with an MCyR had a complete cytogenetic response.

9.3.1. Uncertainties and limitations about favourable effects

A main uncertainty is that only limited efficacy data have been generated in the paediatric target population; The clinical study included only a small sample size of CML patients (N=10). This uncertainty was mitigated by the use of a PK briding strategy where efficacy and safety assumptions in the paediatric population are based on extrapolation from the adult population.

Of note, the paediatric study included non-CML patients. The PK-bridging strategy assumes that the PK in paediatric CML patients can be partly inferred from paediatric patients with other diseases. This is considered an acceptable approach since it can be assumed that there are no clinically relevant PK differences between paediatric patients with CML and the other diseases studied in Study INCB 84344-102.

9.4. Unfavourable effects

The safety data for ponatinib to support the PK bridging and the applied paediatric indication derived from the INCB 84344-102 study, an ongoing, single-arm, Phase 1/2 study of ponatinib monotherapy in paediatric participants, focusing on its CP-CML expansion cohort (n=11, DCO: 25 JAN 2025).

In terms of **TEAEs,** almost all participants (90.9%) in the CP-CML subset were reported to have at least 1 TEAE. The most frequently reported were pyrexia, headache, and thrombocytopenia, neutropenia, nausea, influenza, hypertension, erythema, cough, and abdominal pain.

Grade ≥3 TEAEs were reported for 4 participants (36.4%) in the CP-CML group, included TEAEs of ALT increased, neutropenia, ejection fraction decreased, lipase increased, and platelet count decreased.

SAEs were reported in 3 participants (27.3%) in the CP-CML cohort. Pyrexia and ejection fraction decreased was among the most frequently reported.

No **TEAEs leading to death** were reported in the CP-CML population

TEAEs leading to dose reduction, interruption and treatment discontinuation of ponatinib occurred in two patients with CP-CML due to ejection fraction decreased (treatment discontinuation) and Grade 3 TEAE of lipase increased (dose reduction).

No vascular occlusive events were reported in the overall paediatric populatio. No arterial occlusive eventS occurred in participants with CP-CML. The rate of such events in the entire safety cohort was 1.6%.

ADRs were identified based on results from 61 paediatric participants with R/R leukemias or solid tumors in the study, who received ponatinib monotherapy.

Safety data from INCB 84344-102 study informed the update of the SmPC 4.8. No significant changes besides the change in incidence of some of the grouped terms included already and the addition of new

PT terms under existing (Eye disorders, Cardiac Disorders, Gastrointestinal disorders, Hepatobiliary disorders, Skin and subcutaneous tissue disorders, Reproductive system and breast disorders) and proposed SOCs (Renal and urinary disorders, Investigations). Overall, ADRs are considered adequately described in 4.4. and 4.8 sections of the SmPC.

9.4.1. Uncertainties and limitations about unfavourable effects

Limited safety data have been generated for the proposed posology in paediatric patients. Thus, efficacy and safety assumptions in the paediatric population are based on extrapolation from the adult population via PK bridging, and contingent on matched exposure.

9.5. Benefit-risk assessment and discussion

9.5.1. Importance of favourable and unfavourable effects

This extension of indication application to include the paediatric population (from 6 to 18 years) with CP-CML relies on extrapolation of clinical efficacy and safety, which requires demonstration of comparable plasma exposures in children to those in adults (i.e. exposure matching).

Efficacy and safety data generated in adults can be extrapolated to support paediatric indications for CML provided an adequate PK bridge (exposure matching). This extrapolation is scientifically justified by the shared molecular mechanism of disease, a targeted therapy against the molecular driver of disease, comparable treatment objectives, and similar clinical response patterns observed between adults and children. The extrapolation is complemented by paediatric pharmacokinetic data and some very limited efficacy and safety studies, which confirm that children achieve similar systemic exposure and tolerability at appropriately adjusted dosesThis is supported by EMA guidance (EMEA/CHMP/EWP/147013/2004) and precedents.

The proposed paediatric posology was supported by paediatric PopPK simulations. The PK simulations show that the proposed paediatric posology results in PK exposures comparable to adults.

9.5.2. Balance of benefits and risks

The balance of benefits and risk for the extension of indication of treatment of CP-CML to include patients aged 6 years and older is positive.

9.6. Benefit-risk conclusions

The benefit-risk balance for the treatment of patients aged 6 years and older with CP-CML is positive.