29 January 2026
EMADOC-1700519818-2559402
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Iclusig

International non-proprietary name: Ponatinib

Procedure No. EMA/VR/0000263550

Note

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

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List of abbreviations

Abbreviation	Definition
1L	first-line
ABL1	Abelson proto-oncogene 1
ADR	adverse drug reaction
AE	adverse event
ALL	acute lymphoblastic leukaemia
allo-HSCT	allogeneic haematopoietic stem cell transplantation
ALT	alanine aminotransferase
AOE	arterial occlusive event
AP	accelerated phase
AST	aspartate aminotransferase
BCR	breakpoint cluster region
BM	bone marrow
BP	blast phase
CCyR	complete cytogenetic response
CHR	complete hematologic response
CI	confidence interval
CML	chronic myeloid leukaemia
CMR	complete molecular response
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CSR	Clinical Study Report
CVAD	cyclophosphamide, vincristine, doxorubicin, and dexamethasone
DDI	Drug-drug interaction
DLP	data lock point
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EMA	European Medicines Agency
EOI	end of induction
E-R	exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
GGT	gamma-glutamyltransferase
GIMEMA	Gruppo Italiano Malattie EMatologiche dell'Adulto
HSCT	haematopoietic stem cell transplantation
hyper-CVAD	hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone
IT	intrathecal

Abbreviation	Definition
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MDACC	MD Anderson Cancer Center
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMR	major molecular response
MRD	minimal residual disease
MTX	methotrexate
NCCN	National Comprehensive Cancer Network
NE	not evaluable
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
Ph	Philadelphia chromosome
Ph+ ALL	Philadelphia chromosome–positive acute lymphoblastic leukaemia
PK	pharmacokinetic(s)
PT	preferred term
QD	once daily
QOL	quality of life
RFS	relapse-free survival
RMP	Risk Management Plan
R/R	relapsed/refractory
SAE	serious adverse event
SCS	Summary of Clinical Safety
SCT	stem cell transplantation
SmPC	Summary of Product Characteristics
SOC	system organ class
TEAE	treatment-emergent adverse event
TE-AOE	treatment-emergent arterial occlusive event
TE-VOE	treatment-emergent vascular occlusive event
TE-VTE	treatment-emergent venous thromboembolic event
TKI	tyrosine kinase inhibitor
US	United States
VOE	vascular occlusive event
VTE	venous thromboembolic event
WBC	white blood cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Incyte Biosciences Distribution B.V. submitted to the European Medicines Agency on 28 March 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of adult patients with newly-diagnosed Ph+ ALL for ICLUSIG, based on interim results from study Ponatinib-3001 (PhALLCON); this is a phase 3, randomized, open-label, multicenter study comparing ponatinib versus imatinib, administered in combination with reduced intensity chemotherapy, in patients with newly diagnosed Ph+ ALL; supportive data were derived from two single-arm, open-label clinical studies (AP24534 11 001 in combination with chemotherapy and INCB 84344-201 as monotherapy). As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 23.2 of the RMP has also been submitted. In addition, earlier approved updates were incorporated to the PI.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) EMA/PE/0000261034on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMA/PE/0000261034 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did not seek scientific advice from the CHMP.

1.2. 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

Timetable	Actual dates
Submission date	28 March 2025
Start of procedure	26 April 2025
CHMP Rapporteur's preliminary assessment report circulated on	19 June 2025
CHMP Co-Rapporteur's preliminary assessment circulated on	29 June 2025
PRAC RMP advice and assessment overview adopted by PRAC on	10 July 2025
Joint Rapporteur's updated assessment report circulated on	17 July 2025
Request for supplementary information and extension of timetable adopted by the CHMP on	24 July 2025
MAH's responses submitted to the CHMP on	10 October 2025
Joint Rapporteur's preliminary assessment report on the MAH's responses circulated on	15 January 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on	22 January 2026
CHMP opinion:	29 January 2026
The CHMP adopted a report on similarity of Iclusig with Blincyto, Besponsa, Kymriah and Tecartus on	29 January 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Philadelphia chromosome–positive acute lymphoblastic leukaemia (Ph+ ALL) is a rare malignancy of the blood and bone marrow. Prior to the introduction of tyrosine kinase inhibitors (TKIs), the survival outcomes of Ph+ ALL was poor (Pullarkat et al 2008).

Incorporation of BCR-ABL1 TKIs into chemotherapy regimens has improved survival outcomes (Daver et al 2015, Fielding et al 2014, Ravandi et al 2010, Ravandi et al 2016, Ribera et al 2012). In the EU, imatinib is approved in combination with chemotherapy for first line treatment of adult patients with Ph+ ALL.

Claimed therapeutic indication

The MAH originally sought the indication: "Iclusig is indicated in combination with chemotherapy in adult patients with newly diagnosed Ph+ ALL."

During assessment, the indication was changed to: "Iclusig is indicated in combination with reduced-intensity chemotherapy in adult patients with newly diagnosed Ph+ ALL."

Epidemiology and risk factors

The estimated overall incidence of ALL and lymphoblastic lymphoma in Europe is 1.28 per 1,000, 000 individuals annually (ESMO guidelines 2016) with a peak incidence in children between 2 and 5 years of age (Hoelzer et al 2013). Ph+ ALL constitute 20% to 30% of adult ALL (NCCN 2017, Yanada et al 2009) and is a rare disease. Predisposing risk factors for adult ALL are not known (ESMO guideline 2016).

Biologic features, aetiology and pathogenesis

Ph+ ALL is a malignant proliferation of lymphoid cells characterized by a fusion of the BCR gene on chromosome 22 with the ABL1 gene on chromosome 9. This translocation, referred to as the Philadelphia chromosome, leads to the expression of a BCR ABL1 fusion oncoprotein with constitutive activation of ABL1 tyrosine kinase activity. The deregulated tyrosine kinase activates cell-signalling pathways promoting cell proliferation and survival. The constitutive ABL1 kinase activity is both necessary and sufficient for induction of both Ph+ ALL and chronic myeloid leukaemia (CML) (Deininger et al 2000). Relapse within 1 year after an initial response to a TKI is common and often associated with a BCR-ABL kinase domain point mutation (Gruber et al 2009).

Prognosis

Prior to the introduction of TKIs, the outcome of Ph+ ALL was extremely poor, both in terms of achievement of complete haematological response (CHR) and long-term survival (Pullarkat et al 2008), and the only curative option was allogeneic haematopoietic stem cell transplantation (allo-HSCT) at the earliest opportunity.

The combination of cytotoxic chemotherapy with a TKI (generally imatinib) is now the standard of care for these patients. Despite the high efficacy of such combinations, when second-generation TKIs (such as dasatinib) are used for adult patients with Ph+ ALL, the 3-year relapse-free survival (RFS) was 62% and overall survival (OS) was 69% at best (Ravandi et al 2010, Ravandi et al 2016). However, with an improvement in the rate of complete molecular response (CMR), better survival outcomes have been reported with multiple regimens, including various chemotherapy regimens with TKIs (Chalandon et al 2015, Chiaretti et al 2015, Jabbour et al 2015, Rousselot et al 2016, Schultz et al 2014, Short et al 2016).

Increasing age is a risk factor for the development of Ph+ ALL, and generally the older the age, the worse the prognosis (Chiaretti et al 2015, Hoelzer et al 2016, NCCN 2017).

Management

Treatment

The ESMO has published clinical practice guidelines for treating adults with Ph+ ALL with TKIs, in which it is recommended that a TKI should be administered continuously and should be combined with chemotherapy in first-line (1L) therapy (Hoelzer et al 2016). ESMO interim guideline 2023 specified that reduced-intensity chemotherapy and a first- or second-generation TKI followed by allo-HSCT is considered the standard therapy for newly diagnosed patients.

Although the chemotherapy regimen is not specified, the regimens used in Europe are primarily vincristine, corticosteroids, and an anthracycline (e.g., daunorubicin, doxorubicin, rubidazone, idarubicin), with or without cyclophosphamide or cytarabine. L-asparaginase or pegylated asparaginase could also be included with consolidation that contains methotrexate (MTX) or cytarabine, although a

potential exacerbation of asparaginase-associated toxic effects in patients receiving concomitant TKIs has been reported (Patel et al 2017).

The NCCN guidelines (NCCN 2022) recommend treatment of patients with Ph+ ALL in a clinical trial. If that is not possible, the guidelines then generally recommend 1L treatment of Ph+ ALL with a TKI, along with chemotherapy and/or a steroid.

For elderly patients with comorbidities, age-adjusted chemotherapy or corticosteroids alone have been used with TKIs, and second- or third-generation TKIs are recommended over imatinib (Abou Dalle et al 2019, Mohseni et al 2018, NCCN 2022, Sas et al 2019).

Allogeneic HSCT in the first complete response (CR) is recommended for patients with high risk disease and/or poor molecular response; however, the associated transplant-related mortality and risk of relapse after allo-HSCT remains a significant challenge (Styczyński et al 2020, Warraich et al 2020). A randomized study in which imatinib was given during induction on Days 1 through 14 with low intensity chemotherapy (vincristine plus dexamethasone) or high intensity chemotherapy (hyper CVAD) showed that allogeneic SCT was associated with a statistically significant benefit in RFS and OS. The long-term follow-up results of another study showed that OS was similar among patients with or without allogeneic SCT and that patients with lower levels of residual molecular disease (MMR3-log reduction in BCR-ABL1 transcript levels) at 3 months had improved CR duration with allogeneic SCT (Daver et al 2015).

The role of frontline therapy is still to prepare the patient for HSCT; however, transplantation is an option only available to a subset of patients and is associated with significant rates of both mortality and relapse (Liu Dumlao et al 2012). The role of HSCT in the management of Ph+ ALL has evolved during the last decade. For instance, in patients who received intensive chemotherapy plus a BCR ABL1 TKI and who did not undergo HSCT in first remission, the achievement of CMR within 3 months was the only independent predictor of OS (Short et al 2016), suggesting that highly effective new agents may reduce the reliance on HSCT in first remission (Short et al 2019). Currently, the optimal timing of HSCT is not clear, and eligibility depends on donor availability, depth of remissions, and comorbidities (NCCN 2022).

Unmet medical need

There is an unmet medical need for new treatments that can suppress the development of mutations, thus preventing the sequencing of multiple treatments (including HSCT) and resulting in long-term clinical benefit. When patients with relapsed or refractory Ph+ ALL who received 1L treatment with first- or second-generation TKIs are sequenced to ponatinib, they may develop a second or compound mutation in BCR-ABL1 (Zabriskie et al 2014), some of which may be resistant to all TKIs, including ponatinib (Bauer et al 2013, Khorashad et al 2013, Shah et al 2007, Soverini et al 2021). Options for further treatment with TKIs are then exhausted. The MAH argues that a more potent TKI may result in deeper and more durable responses in the 1L treatment of Ph+ ALL compared with the earlier-generation TKIs, preventing the development of secondary mutations.

The MAH states that a third-generation TKI with a broad spectrum of inhibition and high and durable clinical activity used as frontline therapy could extend the time until transplant and become a valuable alternative to allo-HSCT in noneligible patients. Recent analyses to assess the impact of SCT have not shown a difference in OS by having received allogeneic SCT or not in patients treated with ponatinib plus hyper-CVAD (Kantarjian et al 2023). Thus, investigators speculate that a treatment paradigm shift in Ph+ ALL might occur where allo-HSCT may not be needed, particularly when CMR is achieved (Jabbour et al 2022).

2.1.2. About the product

Ponatinib is a small-molecule TKI designed to optimally 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 (i.e., 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 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.

Ponatinib received accelerated approval from the FDA on 19 March 2024, for the indication claimed in the present application: use in combination with chemotherapy for the treatment of adult patients with newly diagnosed Ph+ ALL. Continued approval is contingent upon verification and description of clinical benefit in a confirmatory trial.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

A similar type II variation to modify the therapeutic indication to include treatment of adult patients with newly diagnosed Ph+ALL was submitted on 22 July 2022 and withdrawn on 11 August 2023 (EMEA/H/C/002695/II/0064). In order to answer the major objection #1, the MAH proposed to include data of Study Ponatinib-3001 (PhALLCON), and to satisfactorily address the list of questions raised by the CHMP, the MAH withdrew the variation and resubmitted the current variation.

This extension of the indication is therefore based upon results of one randomized, open-label clinical study (Ponatinib-3001 PhALLCON) and supported by two single-arm, open-label clinical studies (AP24534-11-001 in combination with chemotherapy and INCB 84344-201 as monotherapy).

2.1.4. General comments on compliance with GCP

The MAH claims that the clinical trials were performed in accordance with GCP.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

No ERA has been submitted with this variation which was considered acceptable.

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable. While a non-clinical overview document has not been provided to discuss the new indication in light of pre-existing non-clinical data, this issue is not pursued as it is considered that there are no new safety aspects that require in-depth discussions.

As presented in the previously approved ERA for Iclusig (dated 29 September 2021), the predicted environmental concentrations in surface water for ponatinib is below the action limit (0.01 µg/L). Therefore, in accordance with the EMA ERA Guideline (EMEA/CHMP/SWP/4447/00 Rev.1-Corr 22 Aug 2024), a phase II assessment is not required. The MAH has committed to submit an updated ERA in the future.

2.2.3. Conclusion on the non-clinical aspects

No non-clinical concerns have been identified that would impact approval.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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.

- Tabular overview of clinical studies

Study Number	Phase	N	Protocol Title	Patient Population	Treatment/Dosing	Status
PIVOTAL STUDY						
Ponatinib-3001 (PhALLCON) NCT03589326 EudraCT 2018-000397-30	3	245	A phase 3, randomized, open-label, multicenter study comparing ponatinib versus imatinib, administered in combination with reduced-intensity chemotherapy, in patients with newly diagnosed Ph+ ALL	Male and female patients aged ≥ 18 years with newly diagnosed Ph+ ALL	Global (all countries except Japan) cohort: Randomized in a 2:1 ratio to receive either ponatinib 30 mg daily, with a dose reduction to 15 mg daily if MRD-negative CR achieved at or after the EOI, or imatinib 600 mg daily; ponatinib and imatinib were administered in combination with 20 cycles of reduced-intensity chemotherapy Japan: all patients were assigned to ponatinib arm only	Ongoing
SUPPORTIVE STUDIES						
AP24534-11-001 (MDACC 2011-0030) NCT01424982	2	87	Phase II study of combination of hyper-CVAD and ponatinib in patients with Philadelphia (Ph) chromosome positive and/or BCR-ABL positive acute lymphoblastic leukemia (ALL)	Adult participants (aged ≥ 18 years) with newly diagnosed Ph+ ALL or with lymphoid CML (AP or BP) that was either previously untreated or previously treated with 1-2 cycles of chemotherapy with or without other TKIs	Ponatinib 45 mg QD for the first 14 days of Cycle 1 and then continuously for subsequent cycles. Ponatinib was administered in combination with 8 cycles of chemotherapy (21 days each), alternating between 2 treatment combinations: hyper-CVAD and high-dose MTX and cytarabine. After 37 participants were treated, the Protocol was amended to reduce the dose of ponatinib to 30 mg/day at Cycle 2, with further reduction to 15 mg once a CMR (defined as absence of quantifiable BCR-ABL1 transcripts) was achieved. A participant could receive maintenance therapy with ponatinib daily (30 or 15 mg) indefinitely.[a]	Completed
INCB 84344-201 (GIMEMA LAL1811) NCT01641107 EudraCT 2012-002761-35	2	44	Front-line treatment of Philadelphia positive (Ph+)/ BCR-ABL positive acute lymphoblastic leukemia (ALL) with ponatinib (INCB084344), a new potent tyrosine kinase inhibitor (TKI). A phase II exploratory multicentric study in patients more than 60 years old or unfit for a program of intensive chemotherapy and stem cell transplantation.	Adult patients with previously untreated Ph+ and/or BCR-ABL+ ALL were either ≥ 60 years old or ≥ 18 years old and unfit for chemotherapy and SCT	Ponatinib 45 mg QD for 6 weeks (defined as 1 course) for 8 courses. Prednisone was administered for 7-14 days before ponatinib. Prednisone was continued for the first 21 days of the first course and then tapered from Day 22 until stopped on Day 29. IT therapy with MTX, cytarabine, and dexamethasone every 28 days was mandatory in participants without clinical cytologic evidence of meningeal involvement. In participants with CNS disease, IT therapy was administered twice weekly until a complete clearance of cerebrospinal fluid blast cells was achieved, once weekly for 4 weeks after that, and once monthly thereafter.	Completed

Note 1: Data cutoff date of 12 AUG 2022 for Study Ponatinib-3001, 14 DEC 2020 for Study AP24534-11-001, and 30 SEP 2021 for Study INCB 84344-201.
Note 2: Study Ponatinib-3001 is a company-sponsored trial; Study AP24534-11-001 was an investigator-sponsored trial; Study INCB 84344-201 was initially an investigator-sponsored trial that transferred to a company-sponsored trial.
[a] Dose reduction was initiated after Protocol Amendment 2.

2.3.2. Pharmacokinetics

Full details of the clinical pharmacology profile of ponatinib, including the effects of intrinsic and extrinsic factors on the PK of ponatinib, have been previously submitted as part of the initial MAA.

Population PK and exposure-response analyses from Study Ponatinib-3001 have been performed with the objectives to estimate the individual PK parameters of ponatinib for patients in Study Ponatinib-3001 based on a previously developed population PK model (i.e., Bayesian re-estimation) and to describe the relationships between ponatinib exposure and efficacy and safety endpoints based on individual predicted ponatinib exposures for patients in Study Ponatinib-3001.

Bioanalysis

The ponatinib concentrations were determined in human plasma containing K3 EDTA as an anticoagulant using solid-phase extraction followed by UPLC with MS/MS detection, for Takeda Development Center Americans, Inc., Sponsor Reference Number Ponatinib-3001. The calibration standard data, QC sample data, ISR data, and chromatograms indicate that the method performed acceptably during the analysis.

Population Pharmacokinetic analysis

Patients randomized to ponatinib received 30 mg of oral ponatinib QD, which was reduced to 15 mg QD if MRD-negative CR was achieved after the end of the induction phase of the study. If a patient lost MRD negativity after dose reduction to 15 mg, re-escalation to 30 mg could be considered after

discussion with the medical monitor/designee. Dose reductions to 15 and 10 mg ponatinib QD were allowed for treatment-emergent toxicities.

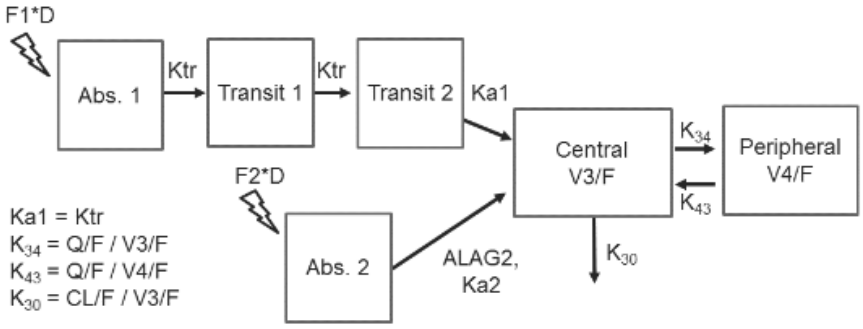
Blood samples were collected during Cycles 1 to 12 of the study to measure plasma concentrations of ponatinib. A predose blood sample was collected prior to dosing on Day 1 of Cycles 1, 2, 3, 4, 6, 9, and 12. Additional samples were collected at 1, 4, and 6 hours postdose on Day 1 of Cycle 2. Additionally, postdose ponatinib PK samples were obtained on Day 14 of Cycles 1 and 2, with 1 sample collected before initiating the vincristine infusion and 1 sample collected after the vincristine infusion before the patient left the clinic. An unscheduled trough sample collection was also to be performed at the first scheduled visit following a dose reduction of at least 7 days duration prior to the visit.

A patient was defined as evaluable if at least 1 dose of ponatinib was administered and at least 1 valid PK sample was recorded in the source clinical data. Concentration samples that were below the lower assay limit of quantitation (BLQ) were kept in the analysis dataset, flagged accordingly, and excluded from the analysis. Data observations for which the absolute value of conditional weighted residuals was greater than 5 (|CWRES| > 5) or with quantifiable concentrations following a large dosing interruption were flagged as "potentially anomalous" and were excluded from the final Bayesian re-estimation.

Individual PK parameter values for patients in Study Ponatinib-3001 were estimated based on the previously developed population PK model (Figure 1). Parameter values (fixed effects and random effects variances) were fixed to the final estimates from the previously developed population PK model with only the individual random effects estimated based on the Study Ponatinib-3001 analysis dataset (i.e., Bayesian re-estimation). Technically, the Bayesian re-estimation was performed by setting initial conditions of the model to values of fixed effects and random effect variances estimated in the previous population PK analysis. This was done using the PsN script "update_inits." Subsequently, the maximum number of estimation iterations was set to 0 by including the string "MAXEVAL=0" in the $ESTIMATION section of the control stream. This requested that the estimation step was omitted, and only the patient-level random effect (η, ETA) values were estimated for each patient. Apart from the adjustment of the control stream described above, no additional model development or adjustment was performed.

Standard diagnostic plots were used to assess the ability of the previously developed population PK model to describe the observed data from Study Ponatinib-3001.

Figure 1. Previously Reported Structural Model Describing the Pharmacokinetics of Ponatinib



Source: [3]

Abbreviations: Abs. 1=first of 2 absorption compartments; Abs. 2=second of 2 absorption compartments; ALAG2=delay in absorption from the second absorption compartment; CL/F=apparent oral clearance; D=dose; F1=fraction of absorbed dose entering in the central compartment circulation via the first absorption compartment; Ka1=first-order absorption rate via F1; Ka2=first-order absorption rate via the second of 2 parallel absorption compartments; Ktr=transit rate constants from the first absorption compartment to the central compartment, identical to Ka1; K30=elimination rate constant from the central compartment; K34 and K43=distributional rate constants between the central and peripheral compartments; Q/F=apparent distributional clearance; V3/F=apparent central volume of distribution; V4/F=apparent peripheral volume of distribution

Table 1. Model Parameters Estimated for the Previously Reported Final Population PK Model for Ponatinib

Parameter	Estimate	Shrinkage
Ka2 (hr^{-1})	4.41	--
CL/F (L/hr)	34.28	--
V3/F (L)	838.6	--
Q/F (L/hr)	17.21	--
V4/F (L)	347.4	--
ALAG2 (hr)	3.932	--
Ka1 (=Ktr) (hr^{-1})	1.302	--
F2 (%)	46.61	--
Age effect on V3/F	$(AGE/49)^{0.6447}$	--
Weight effect on V3/F	$(WT/77.15)^{0.5038}$	--
Interindividual variability (%CV)		
CL/F	48.04	6.422%
V3/F	42.33	19.74%
Ka1	46.85	18.62%
Covariance: CL/F × V3/F	63.68% (correlation)	--
Residual unexplained variability (%CV)		
Healthy volunteers	14.91	12.87%
Patients	38.59	10.35%

Source: Adapted from [3]
Abbreviations: %CV=% coefficient of variation; ALAG2=delay in absorption from the second absorption compartment; CL/F=apparent oral clearance; F2=fraction of absorbed dose entering in the central compartment circulation via the second absorption compartment; Ka1=first-order absorption rate via F1; Ka2=first-order absorption rate via the second of 2 parallel absorption compartments; Ktr=transit rate constants from the first absorption compartment to the central compartment, identical to Ka1; PK=pharmacokinetic; Q/F=apparent distributional clearance; V3/F=apparent central volume of distribution; V4/F=apparent peripheral volume of distribution

The previously reported population PK model included age and body weight as covariates on V3/F. As a result, age and body weight were extracted from the source clinical data for patients in Study Ponatinib-3001 (Table 2).

Table 2. Summary of Individual Baseline Age and Body Weight Values From Study Ponatinib-3001 for Patients Included in the Population PK Analysis Dataset

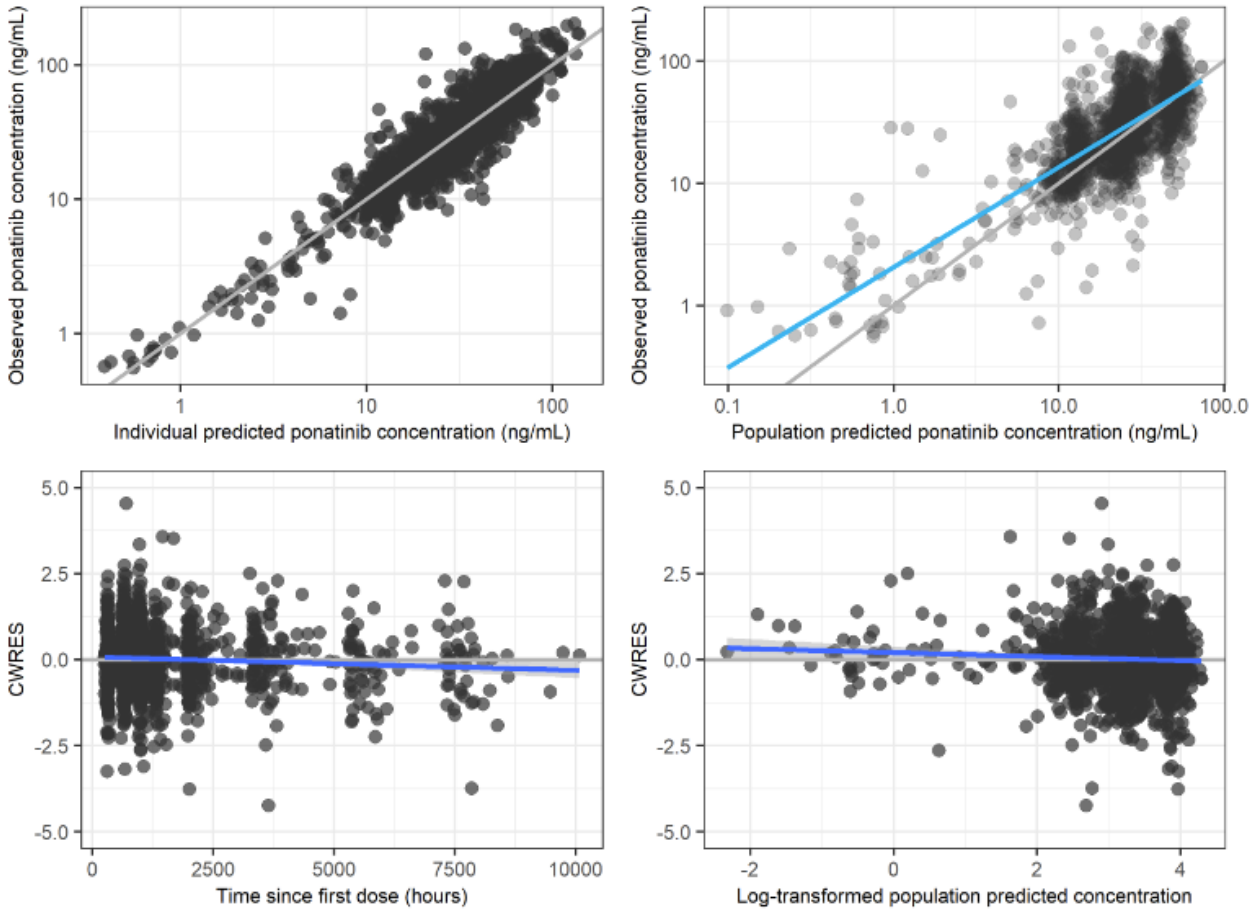
Covariate	N	Missing	Median (Range)
Age (years)	166	0	54.5 (19.0-82.0)
Weight (kg)	166	0	70.1 (39.0-137)

Source: data-exploration-poppk-3001-v4.html, Reference: d468cf:fdc9d4
Abbreviations: N=number of patients; PK=pharmacokinetic

The previously developed population PK model was applied to the PK analysis dataset. The Bayesian re-estimation of the model estimated individual PK parameters using 1630 PK observations from 166 patients treated with ponatinib in the full population PK analysis dataset.

Initial evaluations of goodness-of-fit (GOF) plots of the initial Bayesian re-estimation model identified 2 patients with 1 PK sample each who had large CWRES values (i.e., |CWRES| > 5). Moreover, the initial model identified 3 PK samples with quantifiable concentrations following large dosing interruptions (≥19 days) with very low population-predicted ponatinib concentration. These 5 data points (from 4 patients) were excluded from the final Bayesian re-estimation. Figure 2 shows GOF plots of the final Bayesian re-estimation model.

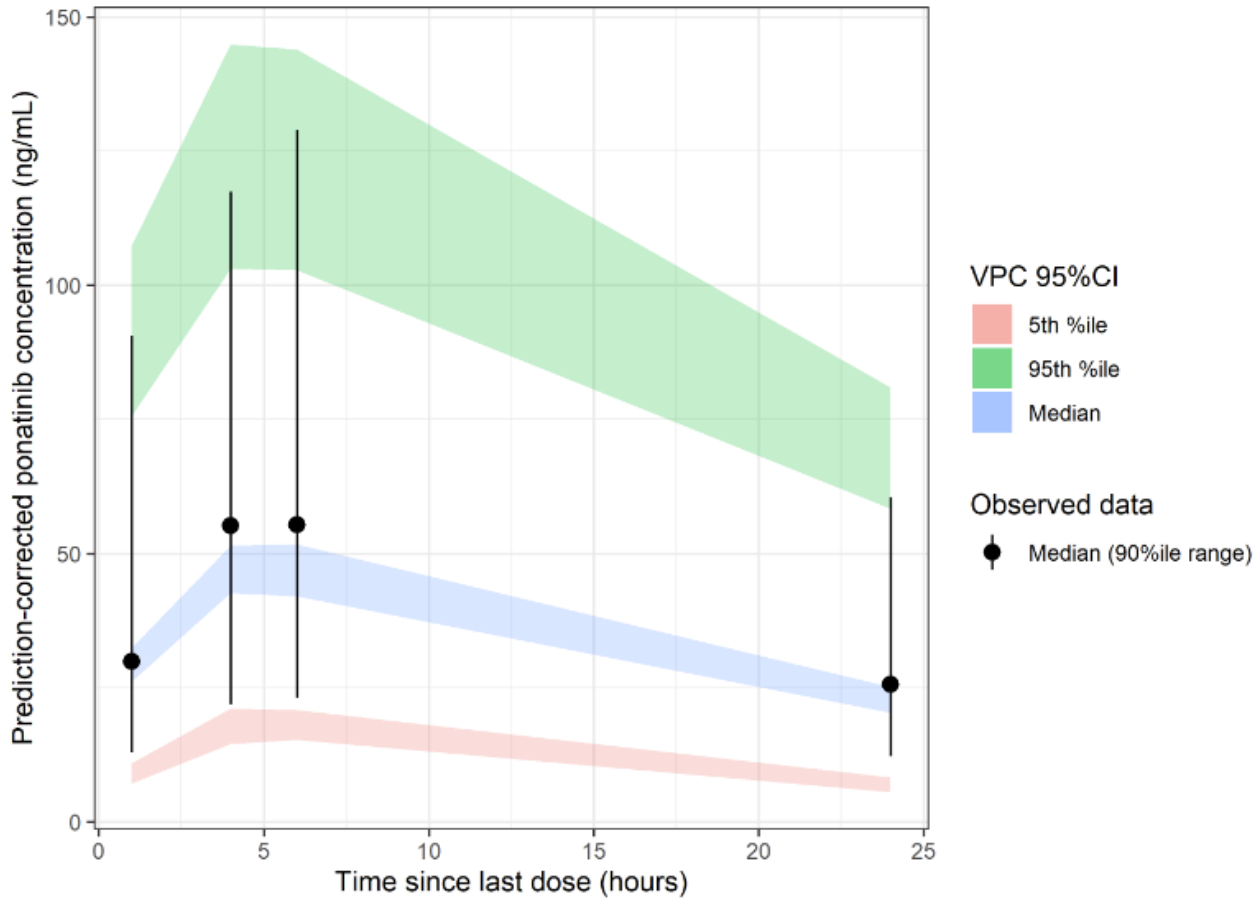
Figure 2. Goodness-of-Fit Plots of the Final Bayesian Re-estimation Model for Study Ponatinib-3001



Source: gof-poppk-3001-v5.html, Reference: 156984:aaaa3e
Notes: The black dots are the individual ponatinib concentrations. The gray line is the line of unity, and the dark blue line and gray shaded area are a linear regression line with 95% confidence interval. The light blue line in the top right panel is a linear regression line.
Abbreviations: CWRES=conditional weighted residuals

A prediction-corrected VPC for the final Bayesian re-estimation model is shown in Figure 3. Model-based predictions from 500 replicates of Study Ponatinib-3001 were compared to the observed data.

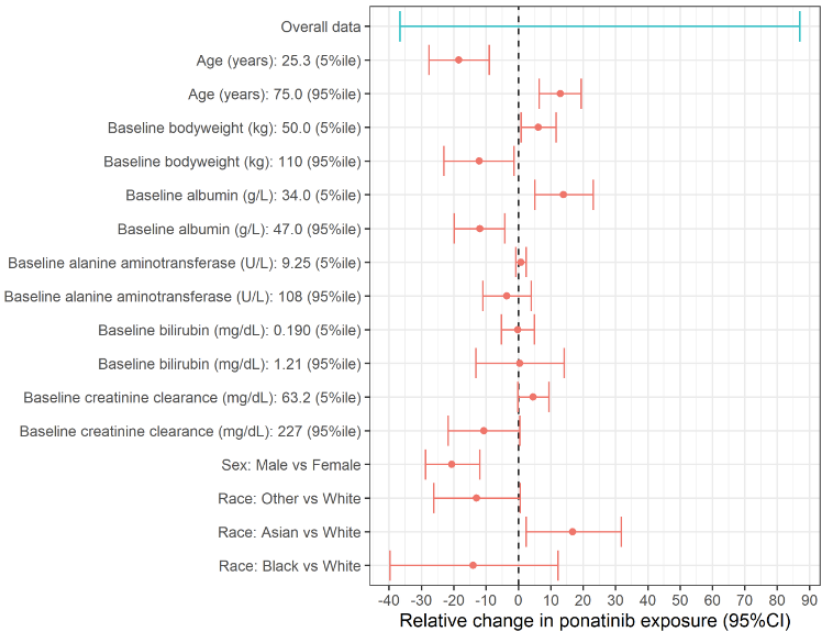
Figure 3. Prediction-Corrected VPC of the Final Bayesian Re-estimation Model



Source: gof-poppk-3001-v5.html, Reference: d350d4:bc6327
Abbreviations: %ile=percentile; CI=confidence interval; VPC=visual predictive check

Based on the Bayesian re-estimation model, the individual predicted exposure following a single oral 30 mg ponatinib dose was calculated based on individual estimated CL/F as area under the concentration-time curve (AUC) = 30 mg/(CL/F). To evaluate potential trends between covariates and individual predicted exposure, AUC was described using linear regression models including individual covariates as predictors. Figure 4 illustrates the magnitude of covariate effects relative to the overall population for ponatinib exposures. Compared with the overall variability in exposure, the magnitude of effects at the 5th and 95th percentiles for continuous covariates or between groups for categorical covariates was not clinically meaningful.

Figure 4. Magnitude of Covariate Effects Relative to the Overall Study Ponatinib-3001 Population on Individual Predicted Ponatinib Exposures



Source: gof-poppk-3001-v5.html, Reference: b2fb6b:be5d13
Notes: The dashed vertical line corresponds to a relative change in ponatinib exposure of 0. The horizontal blue bar shows the 90th percentile range (i.e., 5th to 95th percentile range) of ponatinib exposures relative to the median of individual predicted exposures. Red circles and error bars show exposures and 95% CI at the given covariate values compared with exposure at the median/most common covariate value.
Abbreviations: CI=confidence interval

2.3.3. Pharmacodynamics

Mechanism of action

Ponatinib is a small-molecule TKI designed to optimally 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 (i.e., 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).

2.3.4. PK/PD modelling

The exposure-response (E-R) analysis related ponatinib efficacy and safety endpoints to individual predicted ponatinib exposures (and other potential covariates) based on a binary logistic regression model for efficacy and ordered categorical logistic regression models for safety. The exposure metric used in the analyses was defined as the normalized cumulative exposure (NCE) from the beginning of treatment (i.e., time 0) to a given time after the first dose. This exposure metric was considered in the E-R analyses of both ponatinib efficacy and safety.

A total of 252 patients were considered for inclusion in the E-R analysis dataset based on data availability in the Study Ponatinib-3001 clinical database. One hundred and seventy-one patients were in the ponatinib arm and 81 patients were in the imatinib arm. Five patients who received ponatinib treatment but did not provide any quantifiable PK samples were excluded from all E-R analysis

datasets due to the lack of exposure data. Table 3 shows a summary of the number of patients included in the individual E-R analyses stratified by treatment arm.

Table 3. Summary of the Number of Patients Included in the Exposure-Efficacy and Exposure-Safety Analysis Datasets

E-R Analysis	Ponatinib	Imatinib
MRD-negative CR at the end of induction	150	78
Safety	166	81
Dose reduction or interruption from C1D1 to the end of induction	164	81
Dose reduction or interruption after C4D1	51	11

Source: logistic-regression-safety-3001-v2.html, Reference: 3d7ffe:458b36; logistic-regression-efficacy-3001-v2.html, Reference: 3d7ffe:1f0f81; eda-fdr-3001-v2.html, Reference: 3d7ffe:5dc86e
Abbreviations: C=Cycle; CR=complete response/remission; D=Day; E-R=exposure-response; MRD=minimal residual disease

Covariate Selection for the E-R Models

Base models were developed to assess the relationship between ponatinib exposure and the probability of efficacy and safety responses/events in each of the respective E-R models. If ponatinib exposure was not identified as a statistically significant predictor of response (at p = 0.05), additional covariate analysis was not performed, and the final E-R model was identical to the base model.

The covariates of interest and the specific E-R models (i.e., either efficacy or safety models) in which they were tested were age, body weight, sex, race, transcript type at baseline, ECOG performance status at baseline, prior optional prephase or chemotherapy, baseline platelet count, baseline blasts in the bone marrow, extramedullary disease at baseline and baseline white blood cell count. For the efficacy E-R model for MRD-negative CR at the end of induction, relevant covariates were tested on the intercept. For the safety E-R models, covariates were tested on the baseline logits. For a covariate to be included in the formal covariate analysis, the covariate had to be available in at least approximately 80% of patients. The covariate selection was performed using an iterative forward addition process followed by backward elimination.

Exposure-efficacy

For ponatinib efficacy, the probability of achieving minimal residual disease (MRD)-negative complete response (CR) at the end of induction was related to ponatinib exposure (and possibly other covariates) using a logistic regression model.A total of 35.3% (N=53) of patients given ponatinib achived MRD-negative CR at the end of induction in the analysis dataset.

All patients were given 30 mg once daily during the inductions phase. No statistically significant relationship (p = 0.619) was identified between ponatinib exposure and the probability of achieving MRD-negative CR at the end of induction in the E-R model. Therefore, no additional covariate analysis was performed.

Exposure-safety

Model of Ponatinib Safety

The relationship between ponatinib exposure and the probability of experiencing clinically relevant adverse events (AEs) for patients in Study Ponatinib-3001 was described using an ordered categorical logistic regression model. AEs were considered for the exposure-safety analyses if they occurred from the first day of ponatinib dosing until 30 days after the last dose of ponatinib. For each patient, the DV

in these analyses was the worst grade of AE reported during this period. The AE grades were defined according to the definitions provided by National Cancer Institute Common Toxicity Criteria for Adverse Events Version 5.0. For an AE occurring more than once for a patient, the time to the first occurrence of the worst grade of the AE was used in the analysis. The relationship between ponatinib exposure (NCE) and the probability of experiencing an AE was estimated by a proportional odds logistic regression model. An overview of the treatment-emergent AEs is provided in Table 4.

Table 4. Overview of the Number of Patients in the Ponatinib Arm with Treatment-Emergent AEs Included in the Exposure-Safety Analyses

AE	Grade ≥1	Grade ≥2	Grade ≥3	Grade 4
AOE	4 (2.41%)	3 (1.81%)	2 (1.20%)	0 (0%)
VTE	19 (11.4%)	16 (9.64%)	5 (3.01%)	0 (0%)
Lipase increase	46 (27.7%)	37 (22.3%)	21 (12.7%)	5 (3.01%)
Hypertension	54 (32.5%)	43 (25.9%)	22 (13.3%)	0 (0%)
ALT increase	70 (42.2%)	52 (31.3%)	31 (18.7%)	4 (2.41%)
Thrombocytopenia	77 (46.4%)	76 (45.8%)	74 (44.6%)	68 (41.0%)

Source: logistic-regression-safety-3001-v2.html, Reference: 204133:7499d5
Notes: Values reported as number of AEs (percent).
Abbreviations: AE=adverse events; ALT=alanine aminotransferase; AOE=arterial occlusive event; VTE=venous thromboembolic event

Arterial Occlusive Events

No statistically significant relationship was identified between ponatinib exposure and the probability of experiencing an Arterial Occlusive Events (AOE) (p = 0.202).

Venous Thromboembolic Events

No statistically significant relationship was identified between ponatinib exposure and the probability of experiencing a Venous Thromboembolic Events (VTE) (p = 0.689).

Lipase Increase

No statistically significant relationship was identified between ponatinib exposure and the probability of experiencing lipase increase (p = 0.766).

Hypertension

A statistically significant relationship was identified between ponatinib exposure and the probability of experiencing hypertension with higher exposures associated with a higher probability of experiencing this AE (p = 0.0340). No additional covariates were identified as statistically significant in the subsequent covariate analysis.

ALT Increase

A statistically significant relationship was identified between ponatinib exposure and the probability of experiencing an ALT increase with higher exposures associated with a higher probability of experiencing this AE (p = 0.00340). No additional covariates were identified as statistically significant in the subsequent covariate analysis.

Thrombocytopenia

No statistically significant relationship was identified between ponatinib exposure and the probability of experiencing thrombocytopenia (p = 0.788).

Model of Time to First Adverse Event-Related Dose Reduction or Interruption

The time to first ponatinib dose reduction or interruption due to an AE was analysed in 2 time-to-event (TTE) models.

The first model was based on data from patients treated with the starting dose of 30 mg ponatinib and considered the time from the first ponatinib dose to the end of the induction phase of the study (i.e., the time at which the primary endpoint of the study was assessed). The exposure metric in this model was ponatinib NCE to the time of the first ponatinib dose modification (e.g., reduction, escalation, or interruption) or study discontinuation. Both dose escalation and study discontinuation were considered as right-censoring events.

No statistically significant relationship was identified between ponatinib exposure and the time to first AE-related ponatinib dose reduction or interruption from Cycle 1 Day 1 (C1D1) to the end of induction by the TTE model ($p = 0.321$). Because ponatinib exposure was not identified as a significant predictor in the TTE model, further covariate analysis was not conducted.

The second model considered the time to first ponatinib dose reduction or interruption due to an AE after the induction phase of the study (i.e., after Cycle 4 Day 1 [C4D1]). The exposure metric in the second model was ponatinib NCE from the end of induction to the time of the first AE-related ponatinib dose reduction or interruption. Dose escalation or study discontinuation were considered as right-censoring events. Only efficacy responders who achieved MRD-negative CR at the end of induction and who did not undergo AE-related dose reductions or interruptions during the induction phase were included in the post-C4D1 analysis. Cox proportional hazards TTE models were developed to describe the time to first AE-related dose reduction or interruption from C1D1 to the end of the induction phase and for the post-C4D1 analysis.

A statistically significant relationship was identified between ponatinib exposure and the time to first AE-related ponatinib dose reduction or interruption after C4D1 by the TTE model ($p = 0.0454$). A subsequent covariate analysis was performed, and no covariates were identified as statistically significant.

2.3.5. Discussion on clinical pharmacology

The plasma concentrations of ponatinib for study Ponatinib-3001 were determined using a validated method in accordance with the pertinent guideline.

The MAH used population PK analysis to estimate the individual PK parameters of ponatinib for patients in Study Ponatinib-3001 based on a previously developed population PK model (i.e., Bayesian re-estimation). The ponatinib PK was described by a 2-compartment model with linear first-order elimination from the central compartment. The absorption model for cancer patients consisted of an absorption compartment and 2 sequential transit compartments. A second route of absorption was estimated for healthy volunteers but was not necessary to describe ponatinib PK in cancer patients. The final model of ponatinib PK included body weight and age as covariates on the apparent central volume of distribution (V3/F). Based on the GOF plots the model appears to adequately capture the individual exposures, however, the pcVPC indicates a slight underprediction of higher concentrations. Nevertheless, this is considered a sufficient description of the exposure of ponatinib in patients included in Study Ponaitnib-3001, and the issue was not pursued. A formal covariate analysis was not performed. The evaluation of potential trends between covariates and individual predicted exposure, indicate that there are no clinically relevant effects of the evaluated covariates on ponatinib exposure.

The relationship between ponatinib exposure and the probability of experiencing clinically relevant adverse events (AEs) Arterial Occlusive Events (AOE), Venous Thrombolytic Events (VTE), lipase increase, hypertension, ALT increase, and thrombocytopenia for patients in Study Ponatinib-3001 was analysed. The inability to discern a statistically significant relationship for AOEs, VTEs, lipase increase and thrombocytopaenia may be explained by the limited number of patients experiencing certain AEs. Statistically significant exposure-safety relationships were identified between ponatinib exposure and hypertension (p = 0.0340), and between ponatinib exposure and ALT increase (p = 0.00340), with higher exposures associated with a higher probability of experiencing these AEs.

2.3.6. Conclusions on clinical pharmacology

The PK in patients with newly diagnosed Ph+ ALL was adequately characterised. Ponatinib PK was found to be similar between patients in Study Ponatinib-3001 and patients included in previous population PK analysis.

2.4. Clinical efficacy

2.4.1. Dose response studies

Ponatinib Dose Selection for Evaluation in Study Ponatinib-3001

Clinical information on the safety and efficacy of different doses of ponatinib led to the selection of 30 mg QD as the starting dose for evaluation in Study Ponatinib-3001, with a dose reduction to 15 mg QD upon achievement of MRD-negative CR and re-escalation to 30 mg QD if response was lost. Specifically, a starting dose of ponatinib 30 mg QD for this combination study was based upon consideration of the expected superior benefit-risk balance at 30 mg versus 45 mg QD, which was informed by previously conducted dose intensity-response analyses of data from the phase 1 study AP24534-07-101 and the phase 2 study AP24534-10-201 (PACE). Both studies were conducted in patients with CML and Ph+ ALL.

Logistic regression analyses of dose intensity-AE relationships in participants with chronic phase (CP) CML in the phase 2 Study AP24534-10-201 indicated a dose-dependent increase in AEs, including arterial occlusive events. Dose intensity was a statistically significant predictor of arterial occlusive event rates in that multivariate analysis after adjustment for known cardiovascular risk factors, leading to the expectation that the ponatinib 30 mg QD dose will have a superior safety profile in combination with reduced-intensity chemotherapy compared with 45 mg QD; thus, supporting the selection of the 30 mg QD starting dose for evaluation in Study Ponatinib-3001.

Dose intensity-efficacy logistic regression analyses for Study AP24534-10-201 demonstrated a statistically significant relationship between dose intensity and the probability of achieving MCyR at 12 months. These analyses clearly indicated that 30 mg (vs 15 mg) is within the dynamic range of the inferred dose-response relationship, with the estimated probability of MCyR by 12 months at 30 mg (60%) being meaningfully greater than at 15 mg (≈25%), and both the 30 and 15 mg doses are likely to be pharmacologically active on the basis of data that demonstrated average plasma concentrations exceeding the half maximal inhibitory concentration for all BCR-ABL1 mutations at the 30 mg dose, and for most BCR-ABL1 mutations at the 15 mg dose. Although a direct translation of exposure-efficacy relationships in a resistant CP CML population to a newly diagnosed Ph+ ALL population was not possible, the estimated dose intensity-efficacy relationship in Study AP24534-10-201 nevertheless provided valuable prior information regarding expectations of dose-response relationships for efficacy of ponatinib in BCR-ABL1–driven hematologic malignancies. Accordingly, the results of these analyses

further supported the selection of the 30 mg QD starting dose for ponatinib for evaluation in Study Ponatinib-3001.

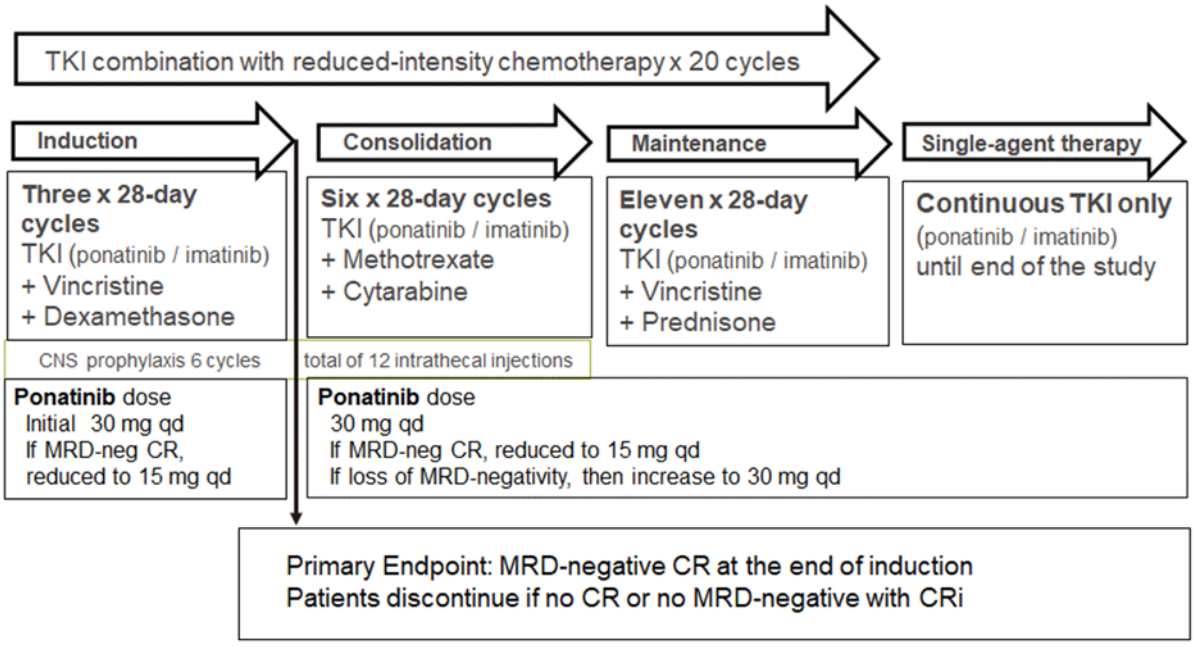
Ponatinib Dose Selection for Evaluation in Phase 2 Studies

The ponatinib dose for treatment of Ph+ ALL (45 mg QD) was selected as the starting dose for Studies AP24534-11-001 and INCB 84344-201. The approved dose was based on the maximum tolerated dose defined in Phase 1 Study AP24534 07 101 and further investigated in Phase 2 Studies AP24534-10-201 and AP24534-14-203. Due to the emergence of cardiovascular AEs in the clinical program, dose reduction was implemented in Study AP24524 11-001 (as of Protocol Amendment 2) after achievement of response to optimize the safety profile without compromising the efficacy of therapy. This approach is similar to the dosing strategy implemented in studies of second- and third-line therapy in participants with CML. In addition, results from Study AP24534-14-203 support maintenance of response at a lower dose, and that the loss of response after dose reduction can be reversed with dose re-escalation.

2.4.2. Main study

***Ponatinib-3001 (PhALLCON): An* ongoing, phase 3, randomized, open-label, multicenter study comparing ponatinib versus imatinib, administered in combination with reduced-intensity chemotherapy, in patients with newly diagnosed Ph+ ALL.**

Figure 5. Ponatinib-3001 Study Design Schema



Methods

Study participants

Patients were randomized at 77 study sites in 17 countries in Asia, Australia, Europe, North America and South America.

Key eligibility criteria

1. Newly diagnosed Ph+ or BCR-ABL1-positive ALL, as defined by the 2017 NCCN guidelines.
2. ≥18 years old (This criterion was revised in country-specific amendments for Argentina and South Korea, for details refer to the CSR Body Section 9.3.1)
3. ECOG performance status ≤ 2.
4. Adequate liver function as defined by the following criteria:

   4.1. Total serum bilirubin ≤1.5× upper limit of normal (ULN), unless due to Gilbert's syndrome.

   4.2. Alanine aminotransferase (ALT) ≤2.5×ULN.

   4.3. Aspartate aminotransferase (AST) ≤2.5×ULN.
5. Adequate pancreatic function as defined by the following criteria:

   5.1. Serum lipase <1.5×ULN.
6. Serum creatinine ≤1.5× the ULN and estimated creatinine clearance ≥30 mL/minute (Cockcroft-Gault formula).
7. Adequate cardiac function as assessed clinically by history and physical examination.

Key exclusion criteria

1. Patients with a history or current diagnosis of chronic phase, accelerated phase, or blast phase CML.
1. Prior/current treatment with any systemic anticancer therapy (including but not limited to any TKI) and/or radiotherapy for ALL, with the exception of an optional prephase therapy or chemotherapy induction (no more than 1 cycle), which was to be discussed with the sponsor's medical monitor/designee.
2. Currently taking drugs that were known to have a risk of causing prolonged QTc or torsades de pointes (TdP) (unless these could be changed to acceptable alternatives or discontinued)
3. Taking any medications or herbal supplements that are known to be strong inhibitors or strong inducers of cytochrome P450 (CYP) 3A4 within at least 14 days before the first dose of study drug
4. Uncontrolled active serious infections that could, in the investigator's opinion, potentially interfere with the completion of treatment according to the protocol.
5. Major surgery within 28 days before randomization (minor surgical procedures such as catheter placement or BM biopsy were not exclusionary criteria).
6. Known HIV seropositivity, known active hepatitis B or C infection.
7. History of acute pancreatitis within 1 year of study screening or history of chronic pancreatitis.
8. Uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL).
9. Diagnosed and treated for another malignancy within 5 years before randomization or previously diagnosed with another malignancy and had any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type were not excluded if they had undergone complete resection.
10. History or presence of clinically relevant CNS pathology such as epilepsy, childhood or adult seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.

11. Clinical manifestations of CNS or extramedullary involvement with ALL other than lymphadenopathy or hepatosplenomegaly.
12. Autoimmune disease with potential CNS involvement.
13. Known significant neuropathy of Grade ≥2 severity.
14. Clinically significant, uncontrolled, or active CV, cerebrovascular, or peripheral vascular disease, or history of or active VTE disease.
15. Poorly controlled diabetes. Patients with pre-existing, well-controlled diabetes were not excluded.

Treatments

Participants were randomized in a 2:1 ratio to receive ponatinib (Cohort A, ponatinib arm) or imatinib (Cohort B, imatinib arm) QD. Both TKIs were administered in combination with reduced-intensity chemotherapy for 3 cycles of induction therapy, 6 cycles of consolidation therapy, and 11 cycles of maintenance therapy, followed by treatment with single-agent ponatinib or imatinib administered continuously after Cycle 20.

Participants randomized to the ponatinib arm received a starting dose of 30 mg ponatinib QD, with a dose reduction to 15 mg QD if they achieved MRD negative CR by the EOI (end of Cycle 3) or later. If a participant had a loss of MRD negativity after a per-Protocol dose reduction to 15 mg, dose re-escalation could be considered after discussion with the sponsor's medical monitor/designee. Participants randomized to the imatinib arm received 600 mg of imatinib QD. A cycle of therapy comprised 28 days of treatment.

Study drug administration continued until the participant was deceased, failed to achieve the primary endpoint of MRD negative CR at the EOI (participants who failed the primary endpoint could remain on study drug at the investigator's discretion if they had achieved CR or MRD negative status with CRi at the EOI), had relapsed from CR or had progressive disease, had an unacceptable toxicity, withdrew consent, proceeded to HSCT or alternative therapy, or the study ended, whichever occurred first.

Objectives

Primary Objective

- Evaluate Efficacy (MRD-Negative CR): To compare the rate of Minimal Residual Disease (MRD)-negative Complete Remission (CR) at the end of the induction phase (end of cycle 3) between the ponatinib and imatinib groups.

Key Secondary Objectives

- Event-Free Survival (EFS): To assess the length of time from randomization to treatment failure, relapse, or death.
- Molecular Response Rates: To measure the depth and duration of response.
- Overall Survival (OS): To evaluate long-term survival outcomes.

Outcomes/endpoints

The **primary endpoint** was MRD-negative CR at the end of induction therapy. The primary endpoint included 2 response components: MRD negativity (defined as ≤ 0.01% BCR-ABL1/ABL1; also referred

to as MR4, or undetectable BCR-ABL1 transcripts in cDNA with ≥ 10,000 ABL1 transcripts; also referred to as CMR) and CR maintained for 4 weeks as recommended by the NCCN ALL guideline at the time of Protocol development (NCCN 2017).

Patients who were MRD-negative CR at baseline, missed MRD assessments from a central laboratory by the end of induction, or discontinued study treatment before the end of induction were considered nonresponders. (None of the patients evaluated after prephase therapy were in MRD-negative CR at baseline).

The **key secondary endpoint** was EFS, defined as the dates of randomization until:

• Death due to any cause.

• Failure to achieve CR by the end of induction.

• Relapse from CR.

Sample size

Assuming an effect size ranging from 20% to 28% (40 - 48% vs. 20% MRD-negative CR rates for the active and control arms, respectively), an upfront committed sample size of approximately 230 patients (approximately 153 vs 77 for the active and control arms, respectively, based on a 2:1 allocation ratio) provided 84% to 98% power for MRD-negative CR at the final analysis (FA) using the efficacy boundary of 0.036 according to the group sequential testing procedure with an interim analysis (IA) performed from 116 patients (Jennison and Turnbull 2000).

Based on 3-year EFS data observed from various phase 2 studies, effect size was assumed as 67% vs 46% for EFS at year 3 for the active and control arms, respectively, or HR=0.516 for non-HSCT patients. The effect size was assumed as 53% and 40% for EFS at year 3 for active and control arms, respectively, or HR=0.693 for patients who are undertaking HSCT. Also, it was assumed that 50% and 45% of patients from active and control arms would undertake HSCT, respectively. Based on simulation studies, approximately 230 patients were enrolled to collect long-term EFS data. Among these 230 patients, approximately 173 events need to be accumulated at final analysis (FA) so that the power was approximately 80% for the EFS endpoint. It was expected that the time of EFS was approximately 8.5 years after first patient had been enrolled.

Randomisation

Patients were randomized in a 2:1 ratio to receive ponatinib or imatinib treatment. The randomization assignment was implemented by IRT. The randomization scheme and codes were provided as a CSR appendix after the formal analysis for EFS.

To adjust for the known confounding factors in the study, patients' randomization assignments were stratified dependent on age: 18 through <45 years; ≥45 through <60 years; and ≥60 years.

Blinding (masking)

The study was open label.

Statistical methods

Analysis populations

The intent-to-treat (ITT) analysis set is defined as all patients who were randomized.

The per-protocol (PP) population is a subset of the ITT population, consisting of all patients who did not violate the terms of the protocol in a way that would affect the study outcome significantly, as determined by the sponsor's medical monitor/designee.

The safety population is defined as all patients who were randomized and received at least 1 dose of any study drug.

Patients at sites in Japan were assigned to the ponatinib arm only. These nonrandomized patients were analyzed separately.

Primary analysis

The primary endpoint is defined as achievement of MRD-negative CR at the end of induction.

Patients who early terminate the study treatment prior to the end of induction were considered as non-responders.

If a C4D1 visit or assessment was not done or not available, then the next available assessment that is completed within 45 days of C3D1 or within 15 days of C4D1 was to be used. If a MRD assessment was not available for C4D1, and if the patient had at least one earlier sample assessed as MRD negative, at least one later sample assessed as MRD negative up to and including C6D1 visit (+7 day window), and no intervening MRD positive results, then that patient was considered to be MRD negative at C4D1.

The primary analysis for MRD-negative CR was conducted using a Cochran-Mantel-Haenszel (CMH) chi-square test, based on the ITT population who have been identified with BCR-ABL1 dominant variants of p190 or p210. The CMH chi-square p-value on risk difference between treatment arms was calculated. The risk difference and relative risk was presented along with 95% 2-sided confidence intervals.

The primary endpoint of MRD-negative CR was first tested at interim analysis (IA) with a 2-sided efficacy boundary of 0.022 in members of the ITT population who had been identified with BCR-ABL1 dominant variants of p190 or p210. The significance boundary for MRD-negative CR was not achieved at the IA; therefore, the study continued until the final analysis (FA) was triggered after the end of induction phase data had been collected for approximately 230 patients. The primary endpoint of MRD-negative CR was tested at the FA with a 2-sided efficacy boundary of 0.036 based on 232 patients.

Sensitivity analyses for the primary endpoint included:

1. MRD-negative CR analyzed in the PP analysis set if more than 5% of patients are excluded from this analysis.

2. After the FA for MRD-negative CR is conducted, an additional sensitivity analysis for the primary endpoint was to be retrospectively performed for the first 150 patients who have been enrolled and treated at the end of induction phase.

Subgroup analyses were performed for the primary endpoint relative to the baseline randomization stratification factor (age); additional age category; demographic data such as gender, race, region; and baseline disease characteristics including BCR-ABL1 Transcript Type and ECOG status.

Key Secondary Efficacy Endpoint

The key secondary endpoint is EFS, defined as the dates of randomization until:

- Death due to any cause.
- Failure to achieve CR by the end of induction.
- Relapse from CR.

According to the SAP, the definition of the EFS event of "failure to achieve CR by the end of induction" is different from the definition of "no CR at the end of induction" used for the primary endpoint. This difference in definitions means that for EFS, patients who did not achieve CR at any time up to the end of induction were counted as having an event of failure to achieve CR by end of induction, and for the primary endpoint, those who achieved CR but did not maintain the response for at least 4 weeks at end of induction were counted as having failure to achieve CR at the end of induction.

The primary analysis for EFS was based on time-to-event analysis. A 2-sided, stratified log-rank test was used to compare the treatment groups with respect to PFS at a 2-sided alpha level of 0.05 for ITT population. An unadjusted stratified Cox model was used to estimate the hazard ratio (HR) and its 95% CIs for the treatment effect using the stratification factor. The primary analysis of EFS did not consider censoring at the time of HSCT or initiation of alternative therapy. Other details regarding the handling of missing assessments and censoring for EFS analysis are presented in the table below.

Table 5: Censoring rules for EFS analysis

Situation	Date of Progression or Censoring	Outcome
Death due to any cause	Date of death	Event
Failure to achieve CR by the end of induction	Day 1	Event
Relapse from CR	Date of documented relapse from CR	Event
No post-randomization CR assessments	Day 1	Event
No documented death or relapse	Date of last adequate assessment*	Censored
Not reached the end of induction	Date of last adequate assessment*	Censored
Lost to follow-up, withdraw consent before any documented death or relapse	Date of last adequate assessment*	Censored

* Adequate disease assessment is defined as there is sufficient data to evaluate a patient's disease status.

Multiplicity

The standard closed sequential testing procedure was used for testing the selected efficacy endpoints with the following testing order.

1. MRD-negative CR rate was tested at the IA and the FA at the significance level determined by the O'Brien-Fleming alpha spending function (the Lan-DeMets method) using the group sequential testing approach. At the IA for MRD-negative CR, alpha spending equaled 0.022 with an efficacy boundary of 0.022 given that 116 patients had been observed. At the FA, alpha spending was 0.028 with an efficacy boundary of 0.036 for MRD-negative CR if the number of patients was 230 (Jennison and Turnbull 2000).

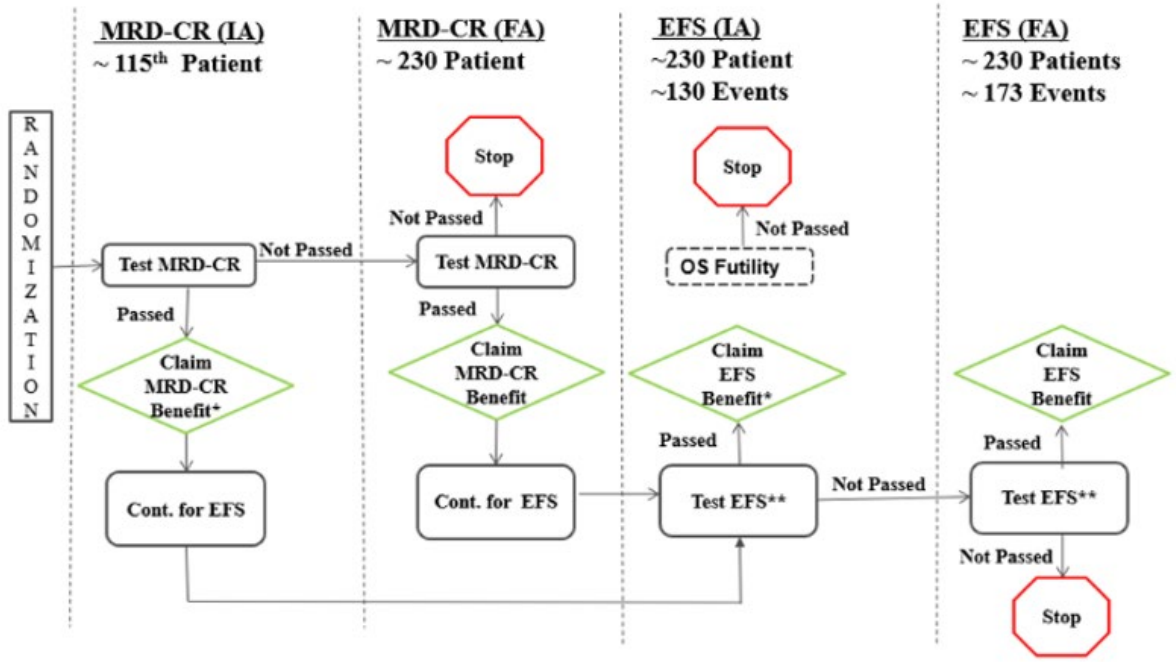
2. EFS was tested only if the primary endpoint comparison achieves statistical significance at the IA or FA for MRD-negative CR. One IA and one FA was planned for EFS: an IA was performed when approximately 130 EFS events were observed (75% of the total 173 expected EFS events). The FA was performed when approximately 173 EFS events had been observed.

EFS was tested at the IA or FA for EFS at the significance level determined by the Gamma Family (-1) alpha spending function using the group sequential testing approach (Hwang et al. 1990). At the IA for EFS, alpha spending is to equal 0.033 with an efficacy boundary of 0.033 for EFS if the observed number of events is 130; at the FA, alpha spending is to equal 0.017 with an efficacy boundary of 0.034 for EFS if the observed number of events is 173.

If the efficacy boundary is crossed at either the IA or FA for EFS, the following endpoints were tested in the order listed below using the same boundaries (0.033 for IA and 0.034 for FA) (Hung et al. 2007):

a) Duration of CR.
b) ORR.
c) Duration of MRD-negative CR.
d) OS.
Therefore, the overall type I error rate for these selected efficacy endpoints was strongly controlled at a 2-sided 0.05 alpha level. The statistical analysis schema is presented below.

Figure 6. Statistical Analysis Schema

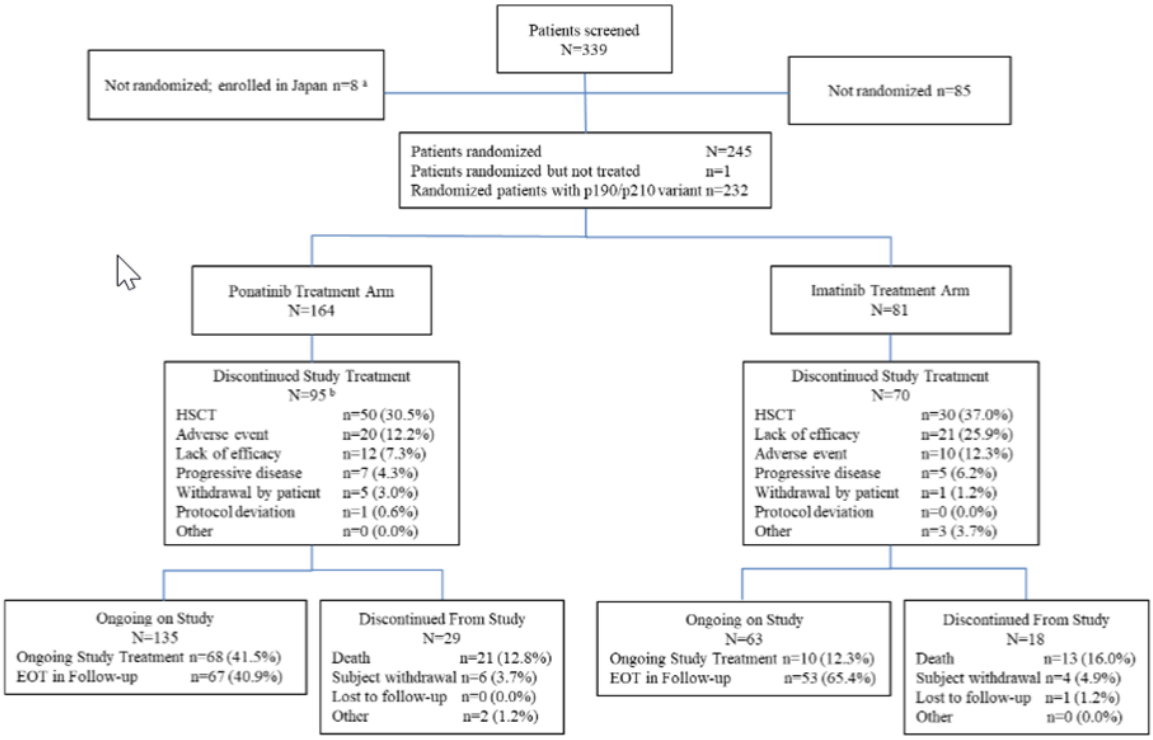


For the secondary endpoint of OS, a futility analysis was conducted at the time of the IA for EFS. The HR and corresponding 95% CI for the OS analysis were calculated and reviewed by the IDMC. If the HR was >1.2, the IDMC reviewed the totality of the data and provided a recommendation to the sponsor's executive committee regarding study continuation.

Results

Participant flow

Table 5. Disposition of Patients



Source: Table 15.1.1.1 and Table 15.1.1.2.

EOT: end-of treatment; HSCT: hematopoietic stem cell transplant.

[a] Patients enrolled in Japan were assigned to the ponatinib treatment arm. One additional Japanese patient was in screening at the time of data cutoff.

[b] One patient discontinued from study before treatment (not counted as discontinued from treatment).

A total of 339 patients were screened, including 9 patients in Japan. (Patients enrolled in Japan were assigned to the ponatinib treatment arm.) Eighty-five (25.1%) patients were screen failures.

The ITT population included a total of 245 patients randomized at 77 study sites in the following regions: 34 patients at 14 sites in APAC (Australia, China, Korea, and Taiwan), 104 patients at 35 sites in Europe (Austria, France, Greece, Italy, Poland, Russia, Spain, and Turkey), 76 patients at 17 sites in North America (Canada, Mexico, and US), and 31 patients at 11 sites in South America (Argentina and Brazil).

Of the 245 patients in the total ITT population, 164 patients (66.9%) were randomized to receive ponatinib 30 mg QD, reduced to 15 mg if MRD-negative CR was achieved at or after the end of induction (ponatinib arm, cohort A), and 81 patients (33.1%) were randomized to receive imatinib 600 mg QD (imatinib arm, cohort B). One patient, randomized to the ponatinib arm, died due to COVID before receiving their first dose of study drug.

The ITT population with a p190/p210 variant (as determined by central laboratory from baseline samples) for the efficacy analyses of the primary endpoint (MRD-negative CR) and the characterization of molecular response (MR4 and MR4.5) included 232 patients (154 patients in the ponatinib arm and

78 patients in the imatinib arm). Thirteen randomized patients were not confirmed to have a p190 or p210 variant (patients either had an atypical variant, had an undetermined dominant variant, or were not tested because no sample was received at the central laboratory) and were not evaluated for the primary endpoint. However, these 13 patients were included in the total ITT population for the analyses of EFS, OS, and the characterization of CR and CRi.

At the time of the FA for the primary endpoint (data cutoff date: 12 August 2022), a higher proportion of patients in the ponatinib arm (41.5%) continued to receive their randomized study treatment than in the imatinib arm (12.3%). Median time on study treatment was longer in the ponatinib arm (7.3 months; range: <1-39 months) than in the imatinib arm (5.1 months; range: <1-41 months).

For patients in the ITT population who stopped taking their randomized study treatment, the most common primary reason for treatment discontinuation overall was HSCT (32.7%), reported in a lower proportion of patients in the ponatinib arm (30.5%) than the imatinib arm (37.0%).

The next most common primary reason for treatment discontinuation was lack of efficacy (13.5%), which was reported for a lower proportion of patients in the ponatinib arm (7.3%) than in the imatinib arm (25.9%). Notably, fewer patients in the ponatinib arm (4.3%) discontinued study treatment due to a failure to achieve MRD negativity than patients in the imatinib arm (18.5%). No difference was observed in the number of patients who discontinued their randomized study treatment due to an AE (12.2% ponatinib arm and 12.3% imatinib arm).

Overall, 34 (13.9%) patients discontinued from the study due to death (12.8% in the ponatinib arm; 16.0% in the imatinib arm).

Recruitment

In this ongoing open-label Phase 3 study, the first participant signed the informed consent form on 04 Oct 2018. The data cutoff date for the final analysis of the primary endpoint was 12 Aug 2022.

Conduct of the study

At the time of the FA for the primary endpoint of MRD-negative CR, this protocol had 6 amendments (excluding country-specific amendments), producing 7 versions of the protocol. Protocol Amendment 10 was in effect at the data cutoff date for the FA of the primary endpoint.

Key changes to each version are summarized below.

Protocol Amendment 1 (Dated 22 May 2018). These changes were applied prior to the inclusion of any patient.

This amendment served the following purposes:

• Provided guidance on imatinib dose modifications for adverse drug reactions.

• Provided guidance on the prevention and management of tumor lysis syndrome.

• Allowed patients with CR who had not achieved MRD-negative CR at the end of induction to remain on-study treatment at the investigator's discretion.

• Increased the planned number of sites because of updated recruitment forecasts.

• Clarified the follow-up of patients who discontinued study treatment.

• Clarified the requirements for patient rescreening.

• Update SAE reporting process and language on monitoring of AEs per updated pharmacovigilance procedure.

Protocol Amendment 2 (Dated 08 November 2018)

This amendment served the following purposes:

• Incorporated advice from the US FDA, including the addition of an endpoint to assess MRD-negative CR at multiple intervals after the end of induction and the addition of timepoints for some other secondary endpoints; corresponding objectives were revised accordingly.

• Incorporated advice from the Spain Ministry of Health (MoH), including the addition of guidance regarding monitoring patients with evidence of prior hepatitis B infections for clinical and laboratory signs of hepatitis B virus reactivation or hepatitis during study treatment as well as the addition of monthly pregnancy testing during study treatment.

• Revised text to reflect inclusion of Japan in the study.

• Updated text based on recent updates to the Takeda Oncology Protocol template, including

addition of a posttrial access section.

Protocol Amendment 4 (Dated 09 May 2019)

The amendment served the following purposes:

• Updated the stratification of randomization criteria to allow for patients to be randomized more proficiently.

• Minor revisions to exclusion criteria.

• Modified assessments on the SOEs to be less of a burden on patients.

Protocol Amendment 8 (Dated 10 February 2021)

The amendment served the following purposes:

• Changed the study design:

– From an adaptive design to a group sequential design for the primary endpoint of MRD-negative CR at the end of induction (CR and BCR-ABL1/ABL1 $\leq$0.01%).

– With the change in design, the max sample size for the FA changed from 230 patients to 150 patients with the addition of an IA at 115 patients.

– To add an IA for event-free survival (EFS).

• Updated the definition for EFS.

• Provided guidance for collecting data, conducting study procedures, and managing investigational product(s) to maintain patient safety, confidentiality, and study integrity during unavoidable circumstances such as the coronavirus disease 2019 (COVID-19) pandemic.

Protocol Amendment 9 (Dated 07 May 2021)

The amendment served the following purpose:

• Clarified that the BCR-ABL1/ABL1 MRD assessment was to be conducted using the same methodology in more than 1 central laboratory due to local regulations that prohibit shipping of biological samples.

Protocol Amendment 10 (Dated 20 October 2021)

The amendment served the following purpose:

• Updated the efficacy analysis to reflect a change in the sample size for the FA from 150 patients to 230 patients, the total enrollment planned.

In addition, the amendment:

• Clarified that patients who achieved MRD-negative status with CRi at the end of induction could remain on study drug treatment, at the investigator's discretion.

• Clarified that for MRD-negative CR, the analysis would be based on the ITT population who have been identified with BCR-ABL1 dominant variants of p190 or p210.

• Provided additional guidance to sites regarding survival follow-up assessments, timing for EOT, reporting of mutation status if available at time of relapse, and the time period for requiring BM at EOT.

Protocol deviations

As of the data cutoff, a total of 32 patients had at least 1 significant protocol deviation identified. The proportion of patients with at least 1 significant protocol deviation was similar in the ponatinib arm (13.5%) and the imatinib arm (12.3%).

Baseline data

Demographic characteristics for participants in the ITT population were well balanced across treatment arms and consistent across the stratification factor. The median age of participants was 54.0 years. The majority of participants were female and White, consistent with expectations for a study population of patients with newly diagnosed Ph+ ALL. Most participants were enrolled at sites in Europe.

Table 7. Study Ponatinib 3001 Key Baseline Participant Characteristics by Treatment Arm (ITT Population)

	Ponatinib Arm (Cohort A) N = 164	Imatinib Arm (Cohort B) N = 81
Age (years)[a]		
n	164	81
Mean (STD)	51.2 (16.09)	50.6 (14.60)
Median	54.0	52.0
Min, max	19, 82	19, 75
Stratification factor n (%)[a]		
Age category		
18-< 45	58 (35.4)	29 (35.8)
45-< 60	45 (27.4)	22 (27.2)
≥ 60	61 (37.2)	30 (37.0)
Gender n (%)		
Male	74 (45.1)	38 (46.9)
Female	90 (54.9)	43 (53.1)
Race n (%)		
White	104 (63.4)	62 (76.5)
Asian	20 (12.2)	11 (13.6)
Black or African American	9 (5.5)	4 (4.9)
American Indian or Alaska Native	2 (1.2)	2 (2.5)
Native Hawaiian or other Pacific Islander	0	0
Multiple	1 (0.6)	0
Not reported	28 (17.1)	2 (2.5)
Region n (%)		
Europe	71 (43.3)	33 (40.7)
North America	50 (30.5)	26 (32.1)
APAC	22 (13.4)	12 (14.8)
South America	21 (12.8)	10 (12.3)

Note: Asia Pacific comprises all of Asia and Oceania.
[a] Participants' randomization was stratified dependent on age category per interactive response system data.
Source: Ponatinib-3001 CSR Table 15.1.4.1.

Source: Summary of Clinical Efficacy 2.1.4.2.

Baseline disease characteristics were balanced between the treatment arms for the ITT population. Most participants entered the study with an ECOG performance status score of 0 or 1 and without extramedullary disease. Participants in the ponatinib arm had a slightly higher disease burden compared to those in the imatinib arm, with median BM blast counts of 80.0% in the ponatinib arm compared to 75.0% in the imatinib arm.

The proportions of participants with a baseline p190 or p210 BCR-ABL1 variant were similar to those reported in literature (Nashed et al 2003), with the majority of participants (68.2%) having the p190 BCR-ABL1 variant.

Table 8. Study Ponatinib 3001 Key Baseline Disease Characteristics by Treatment Arm (ITT Population)

	Ponatinib Arm (Cohort A) N = 164	Imatinib Arm (Cohort B) N = 81
ECOG score n (%)		
0	72 (43.9)	33 (40.7)
1	85 (51.8)	43 (53.1)
2	7 (4.3)	5 (6.2)
≥ 3	0	0
Baseline leukemic blasts (%)		
n	146	75
Mean (STD)	68.58 (28.552)	64.72 (31.164)
Median	80.00	75.00
Min, max	0.0, 100.0	0.0, 100.0
BCR-ABL1 dominant variants n (%)		
p190	114 (69.5)	53 (65.4)
p210	40 (24.4)	25 (30.9)
Atypical	0	1 (1.2)
Undetermined/not tested[a]	10 (6.1)	2 (2.5)
Time since Ph+ ALL diagnosis (days)		
n	163	81
Mean (STD)	15.1 (9.94)	15.8 (12.99)
Median	12.0	12.0
Min, max	2, 63	2, 105
Prephase therapy n (%)		
Yes	74 (45.1)	41 (50.6)
No	90 (54.9)	40 (49.4)
Duration of prephase therapy (days)		
n	73	41
Mean (STD)	10.9 (9.18)	8.7 (6.48)
Median	8.0	7.0
Min, max	1, 42	1, 35
Presence of extramedullary disease n (%)		
Yes	10 (6.1)	3 (3.7)
No	154 (93.9)	78 (96.3)

Note: Baseline was defined as the last observation before first dose of study drug. Prephase therapy was an optional prephase therapy or chemotherapy induction (no more than 1 cycle), excluding TKI, that was allowed per Protocol.
[a] "Undetermined" was defined as samples were assessed but no BCR-ABL1 dominant variant determined at the central laboratory. "Not tested" was defined as samples not received at the central laboratory.
Source: Ponatinib-3001 CSR Table 15.1.4.2.1.

Source: Summary of Clinical Efficacy 2.1.4.2.

Prior Treatments

46.9% of participants had received prephase anticancer therapy as permitted by the protocol. Optional prephase therapy or chemotherapy induction (no more than 1 cycle) excluding TKI, was permitted by the Protocol. Duration of prephase therapy was similar between the 2 arms, 8 (ponatinib arm) vs 7 (imatinib arm) days.

Table 9. Study Ponatinib 3001 Best Prephase Therapy Response

	Ponatinib Arm (Cohort A) (N=164)	Imatinib Arm (Cohort B) (N=81)	Total (N=245)
Best Prephase Therapy Response [n (%)] [b]			
Complete Response (CR)	3 (4.1)	1 (2.4)	4 (3.5)
Incomplete CR (CRi)	4 (5.4)	1 (2.4)	5 (4.3)
CR with deep molecular response (MR4 or better)	0	0	0
Progressive Disease (PD)	0	0	0
Unable to Assess (UA)	23 (31.1)	16 (39.0)	39 (33.9)
Unknown	34 (45.9)	16 (39.0)	50 (43.5)
Other	9 (12.2)	6 (14.6)	15 (13.0)
Missing	1	1	2

Prephase Therapy is an optional prephase therapy or chemotherapy induction (no more than 1 cycle) excluding TKI that is allowed per protocol.
[b] Percentages are calculated out of the total number of subjects who received prephase therapy.

Numbers analysed

For definitions of analysis populations, refer to section "Statistical Methods".

Table 10: Analysis populations

	Ponatinib Arm (Cohort A) N=164 n (%)	Imatinib Arm (Cohort B) N=81 n (%)	Total N=245 n (%)
ITT population	164 (100)	81 (100)	245 (100)
ITT population with p190/p210 variant	154 (93.9)	78 (96.3)	232 (94.7)
Safety population	163 (99.4)	81 (100)	244 (99.6)
Per-protocol population	163 (99.4)	81 (100)	244 (99.6)
Patients randomized but not treated [a]	1 (0.6)	0	1 (0.4)
Patients randomized and treated	163 (99.4)	81 (100)	244 (99.6)

Outcomes and estimation

Primary Efficacy Endpoint: MRD-Negative CR at the End of Induction

The primary efficacy analysis was conducted using the composite endpoint of MRD-negative CR at the EOI in the ITT population, with a p190 or p210 dominant variant identified through central laboratory tests. At the time of the FA for the primary endpoint, among the 232 participants in the ITT population with a baseline p190 or p210 variant, the MRD-negative CR rate at EOI for ponatinib (34.4%) was statistically significantly higher compared to imatinib (16.7%) with a p value of 0.0021 (Table 11).

Table 11. Study Ponatinib-3001 Primary Analysis of MRD-Negative CR by Treatment Arm at the End of Induction (ITT Population With p190/p210 Variant)

	Ponatinib Arm (Cohort A) N = 154	**Imatinib Arm (Cohort B) N = 78**
MRD-negative CR status at the end of induction	154	78
Achieved n (%)	53 (34.4)	13 (16.7)
Did not achieve n (%)	101 (65.6)	65 (83.3)
Risk difference (95% CI)[a]	0.18 (0.06, 0.29)	
p-value[b]	0.0021	
Relative risk (95% CI)[c]	2.06 (1.19, 3.56)	

Note 1: A participant with MRD-negative CR (≤0.01% BCR-ABL1/ABL1 or undetectable BCR-ABL1 transcripts in cDNA with ≥ 10,000 ABL1 transcripts, and meeting criteria for CR) at the end of induction was considered to have achieved the primary endpoint. Participants who were missing MRD assessments from the central laboratory by the end of induction or terminated study treatment prior to the end of induction were considered to have not achieved the primary endpoint.

Note 2: If a C4D1 visit or assessment was not done or not available (eg, participant discontinues after C3D28 or had a C4D1 dry tap BM at C4D1), then the next available assessment that was completed within 45 days of C3D1 or within 15 days of C4D1 (ie, "EOT" or "Unscheduled" visit) was used.

[a] Risk difference and 95% CI: adjusted percent ponatinib - adjusted percent imatinib and its 95% CI.

[b] P-value is based on CMH chi-square test, with stratification according to randomization strata (age): 18 through < 45 years, ≥ 45 through < 60 years, and ≥ 60 years.

[c] Adjusted relative risk and its 95% CI based on CMH method as defined in footnote b.

Source: Ponatinib-3001 CSR Table 15.2.1.1.

101 and 65 (ponatinib and imatinib arm) patients did not reach MRD-negative CR-status at the end of induction. Out of them 67 and 43 (ponatinib and imatinib arm) reached CR.

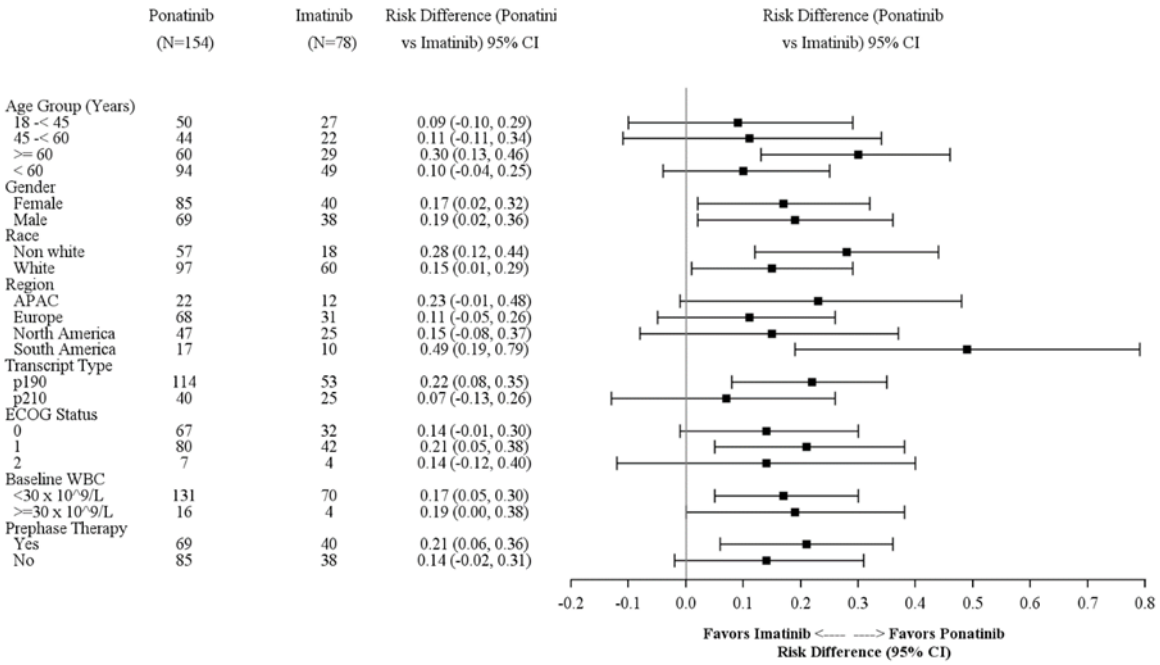
Table 12. Study Ponatinib-3001 MRD-Negative CR Status by Treatment Arm at the End of Induction (ITT Population With p190/p210 Variant)

	Ponatinib Arm (Cohort A) (N=154)	Imatinib Arm (Cohort B) (N=78)
Did not Complete Induction Phase	7 (4.5)	9 (11.5)
Completed Induction Phase [a]	147 (95.5)	69 (88.5)
MRD-negative CR Status at the End of Induction n (%)		
Achieved MRD-negativity (<=0.01%)	64 (41.6)	16 (20.5)
CR*	53 (34.4)	13 (16.7)
Non CR	11 (7.1)	3 (3.8)
Achieved MR4.5 (<=0.0032%)	39 (25.3)	10 (12.8)
Did not Achieve MRD-negativity	83 (53.9)	53 (67.9)
CR*	67 (43.5)	43 (55.1)
Non CR	16 (10.4)	10 (12.8)

Note: MRD-negativity is defined as a molecular response 4-log reduction (BCR-ABL1/ABL1<=0.01%, with ABL1 ≥ 10000 copies).
Note: Patients with p190/p210 variants are identified by central lab.
Note: * Meet all CR criteria for at least 4 weeks.
Note: Percentages are calculated out of the total number of subjects.
[a] Subjects with completion of induction phase included subjects who did not early terminate treatment before end of induction phase (subjects who have EOT efficacy assessments within end of induction phase window were considered completing induction phase)

Subgroup Analysis for the Primary Endpoint

Figure 7. Study Ponatinib-3001 Subgroup Analysis for MRD-Negative CR Rates Achieved at the End of Induction by Treatment Arm (ITT Population With p190/p210 Variant)



Source: Ponatinib 3001 CSR Figure 15.2.1.2

Key Secondary Efficacy Endpoint: Event-free Survival

The key secondary endpoint of EFS was defined as the date of randomization until death due to any cause, failure to achieve CR by the EOI, or relapse from CR. At the time of the data cutoff, EFS was not formally tested as the prespecified number of events (130) for analysis had not been reached.

As of the data cutoff, 58 (44.6%) of the 130 required EFS events were reported, including 34 (20.7%) in the ponatinib arm and 24 (29.6%) in the imatinib arm. Median follow-up for EFS was 17.32 months (95% CI: 15.39, 20.57) in the ponatinib arm and 15.86 months (95% CI: 10.82, 22.21) in the imatinib arm.

Median EFS was not reached for the ponatinib arm and was 29.04 months (95% CI: 22.29, NE) for the imatinib arm. Of note, relapse from CR was a major contributor to EFS in either arm. A 34.8% reduction in the risk of experiencing an EFS event was reported in the ponatinib arm with an HR of 0.652 (95% CI: 0.385, 1.104).

The KM curve of EFS appears to start separating after consolidation therapy (at approximately 12 months) and further separation continues with time. KM estimates at 24 months for EFS were higher in the ponatinib arm (71.6% [95% CI: 60.9, 79.8; n = 38]) than in the imatinib arm (59.8% [95% CI: 43.1, 73.1; n = 17]).

Table 13. Study Ponatinib-3001 Analysis of Key Secondary Endpoint of Event-Free Survival by Treatment Arm (ITT Population)

	Ponatinib Arm (Cohort A) N = 164	Imatinib Arm (Cohort B) N = 81
Number with events n (%)	34 (20.7)	24 (29.6)
Death due to any cause	11 (6.7)	7 (8.6)
Failure to achieve CR by EOI	6 (3.7)	3 (3.7)
Relapse from CR	14 (8.5)	12 (14.8)
No postrandomization CR assessments	3 (1.8)	2 (2.5)
Number of censored n (%)	130 (79.3)	57 (70.4)
25th percentile (95% CI) (months)[a]	23.39 (15.89, NE)	20.07 (11.54, 23.54)
Median time (95% CI) (months)[a]	NE (NE, NE)	29.04 (22.29, NE)
75th percentile (95% CI) (months)[a]	NE (NE, NE)	NE (32.46, NE)
Min, max (months)[b]	0.04, 44.54*	0.04, 38.64*
KM estimate (95% CI) [no. at risk]		
3 months	92.7 (87.4, 95.8) [n = 151]	93.8 (85.8, 97.4) [n = 72]
6 months	90.5 (84.7, 94.2) [n = 116]	89.4 (79.7, 94.6) [n = 57]
9 months	87.3 (80.7, 91.8) [n = 104]	85.9 (75.2, 92.2) [n = 46]
12 months	86.4 (79.6, 91.1) [n = 89]	81.8 (69.8, 89.4) [n = 40]
15 months	84.4 (77.1, 89.6) [n = 83]	77.6 (64.6, 86.3) [n = 33]
18 months	81.1 (72.9, 87.0) [n = 66]	75.1 (61.4, 84.5) [n = 28]
21 months	78.3 (69.3, 84.9) [n = 50]	69.6 (54.6, 80.4) [n = 24]
24 months	71.6 (60.9, 79.8) [n = 38]	59.8 (43.1, 73.1) [n = 17]
27 months	65.7 (53.7, 75.2) [n = 23]	51.8 (34.2, 66.9) [n = 11]
30 months	65.7 (53.7, 75.2) [n = 18]	46.7 (28.4, 63.0) [n = 9]
33 months	65.7 (53.7, 75.2) [n = 9]	38.9 (19.3, 58.1) [n = 5]
36 months	65.7 (53.7, 75.2) [n = 5]	38.9 (19.3, 58.1) [n = 2]
Median (95% CI) of follow-up (months)	17.32 (15.39, 20.57)	15.86 (10.82, 22.21)
The primary reason of censoring n (%)		
Death or relapse not documented	123 (75.0)	49 (60.5)
Lost to follow-up or withdrew consent before any documented death or disease progression	5 (3.0)	2 (2.5)
Did not reach EOI	2 (1.2)	6 (7.4)
HR (95% CI)[c]		
Treatment group: ponatinib vs imatinib arm	0.652 (0.385, 1.104)	—

Note: Event-free survival is defined as from the dates of randomization until death due to any cause, or failure to achieve CR by the EOI, or relapse from CR.

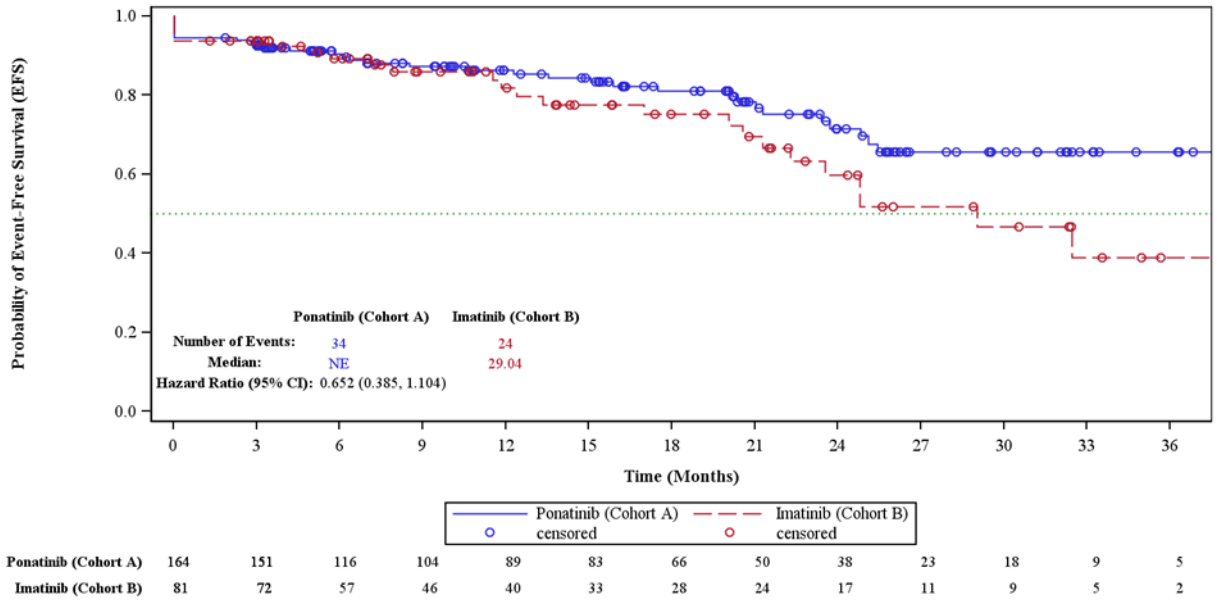
[a] Quartile time and 95% CI are estimated based on KM product limit.

[b] Censored values are denoted by an asterisk (*) and only nonmissing values are used.

[c] Stratified Cox regression model using stratification according to randomization strata (age): 18 through < 45 years, ≥ 45 through < 60 years, and ≥ 60 years.

Source: Ponatinib-3001 CSR Table 15.2.2.1.1.

Figure 8. Study Ponatinib 3001 Kaplan-Meier Plot of Event-free Survival (ITT Population)



Source: Summary of clinical efficacy 2.7.3

OS

OS analysis was based on a limited number of death events at the time of the data cutoff (34 of 245 events, 13.9% overall). There were 21 (12.8%) events in the ponatinib arm and 13 (16.0%) events in the imatinib arm. Median OS was not reached for either treatment arm. Median follow-up period on study was 20.43 months (95% CI: 18.39, 23.93) for the ponatinib arm and 18.14 months (95% CI: 13.86, 24.25) for the imatinib arm.

Table 14: Analysis of Overall Survival by Treatment Group ITT Population

	Ponatinib Arm (Cohort A) (N=164)	Imatinib Arm (Cohort B) (N=81)
Number with Events [n(%)]	21 (12.8)	13 (16.0)
Number of Censored [n(%)]	143 (87.2)	68 (84.0)
25th Percentile (95% CI) (Months) [a]	NE (23.71, NE)	28.18 (22.29, NE)
Median Time (95% CI) (Months) [a]	NE (NE , NE)	NE (29.04, NE)
75th Percentile (95% CI) (Months) [a]	NE (NE , NE)	NE (NE , NE)
Min, Max (Months) [b]	0.25, 44.54*	0.29, 44.11*
Median (95%CI) of Follow up (Months)	20.43 (18.39,23.93)	18.14 (13.86,24.25)
Hazard Ratio (95% CI) [c]		
Treatment Group: Ponatinib vs Imatinib Arm	0.761 (0.381, 1.520)	

Note: Overall Survival is defined as the interval between the time of randomization and death due to any cause.
[a] Quartile time and 95% CI are estimated based on Kaplan-Meier product limit.
[b] Censored values are denoted by an asterisk (*) and only non-missing values are used.
[c] Stratified Cox regression model using stratification according to randomization strata (age): 18 through <45 years, >=45 through <60 years, and >=60 years.

Ancillary analyses

Only the primary endpoint was type 1 error controlled.

Sensitivity Analysis for the Primary Endpoint

The sample size of 230 patients was initially planned but has been changed during the study. Prior to the interim analysis of the primary endpoint, the planned sample size was decreased to 150 patients (protocol amendment 8), then increased again to 230 patients (protocol amendment 10). The anticipated efficacy estimate varied in the sample size calculations; from the initial 28% difference in MRD-negative rates to a range of 20% to 28% in the final calculation. A sensitivity analysis for the primary endpoint was performed for the first 150 enrolled patients.

Table 15. Sensitivity Analysis 4 of MRD-negative CR by Treatment Arm at the End of Induction ITT Population with p190/p210 Variant (First 150 Patients Enrolled)

	Ponatinib Arm (Cohort A) (N=100)	Imatinib Arm (Cohort B) (N=50)
MRD-negative CR status at the End of Induction	100	50
Achieved [n (%)]	36 (36.0)	10 (20.0)
Did not achieve [n (%)]	64 (64.0)	40 (80.0)
Risk Difference (95% CI) [a]	0.16 (0.01, 0.31)	
p-value [b]	0.0311	
Relative Risk (95% CI) [c]	1.81 (0.97, 3.36)	

Note: A patient with MRD-negative CR (<=0.01% BCR-ABL1/ABL1 or undetectable BCR-ABL1 transcripts in cDNA with >=10,000 ABL1 transcripts and meet the criteria for CR) at the end of induction is considered to have achieved the primary endpoint. The patients who are missing MRD assessments from the central laboratory by the end of induction, or terminate study treatment prior to the end of induction will be considered to have not achieved the primary endpoint.
[a] Difference and 95% CI: adjusted percent ponatinib - adjusted percent imatinib and its 95% CI.
[b] P-value is based on Cochran-Mantel-Haenszel (CMH) chi-square test, with stratification according to randomization strata (age): 18 through <45 years, >=45 through <60 years, and >=60 years.
[c] Adjusted Relative Risk and its 95% CI based on CMH method as defined in Footnote [b].
Percentages are based on the first 150 patients who have been enrolled and treated by the end of induction phase and have been identified with BCR-ABL1 dominant variants of p190 or p210.
Patients with p190/p210 variants are identified by central lab.

Other Secondary Efficacy Endpoints

Rates of MRD-Negative CR at Multiple Intervals After the End of Induction

Different from the primary endpoint, noncumulative rates of MRD-negative CR that were achieved or maintained at the end of each cycle are reported for participants in the ITT population with a p190 or p210 variant who had an MRD and/or CR assessment available within the Protocol-defined window of ± 7 days from the scheduled visit.

Substantially higher rates of MRD-negative CR were achieved at the end of Cycle 3 for participants in the ponatinib arm compared to those in the imatinib arm. At subsequent time points, higher rates of MRD-negative CR were reported for the ponatinib arm compared to the imatinib arm, with the largest difference in MRD-negative CR (77.4% in the ponatinib arm compared to 18.8% in the imatinib arm) reported at the end of Cycle 9.

Table 16. Study Ponatinib-3001 Rates of MRD-Negative CR by Treatment Arm at the End of Treatment Cycles (ITT Population With p190/p210 Variant)

	Ponatinib Arm (Cohort A) N = 154	**Imatinib Arm (Cohort B) N = 78**
At the end of Cycle 3, Induction Phase	148	71
MRD-negative CR rate[a] n (%)	57 (38.5)	13 (18.3)
95% CI[b]	(30.6, 46.9)	(10.1, 29.3)
At the end of Cycle 5, Consolidation Phase	100	35
MRD-negative CR rate[a] n (%)	37 (37.0)	11 (31.4)
95% CI[b]	(27.6, 47.2)	(16.9, 49.3)
At the end of Cycle 7, Consolidation Phase	69	24
MRD-negative CR rate[a] n (%)	24 (34.8)	6 (25.0)
95% CI[b]	(23.7, 47.2)	(9.8, 46.7)
At the end of Cycle 9, Consolidation Phase	53	16
MRD-negative CR rate[a] n (%)	41 (77.4)	3 (18.8)
95% CI[b]	(63.8, 87.7)	(4.0, 45.6)
At EOT	76	56
MRD-negative CR rate[a] n (%)	19 (25.0)	11 (19.6)
95% CI[b]	(15.8, 36.3)	(10.2, 32.4)

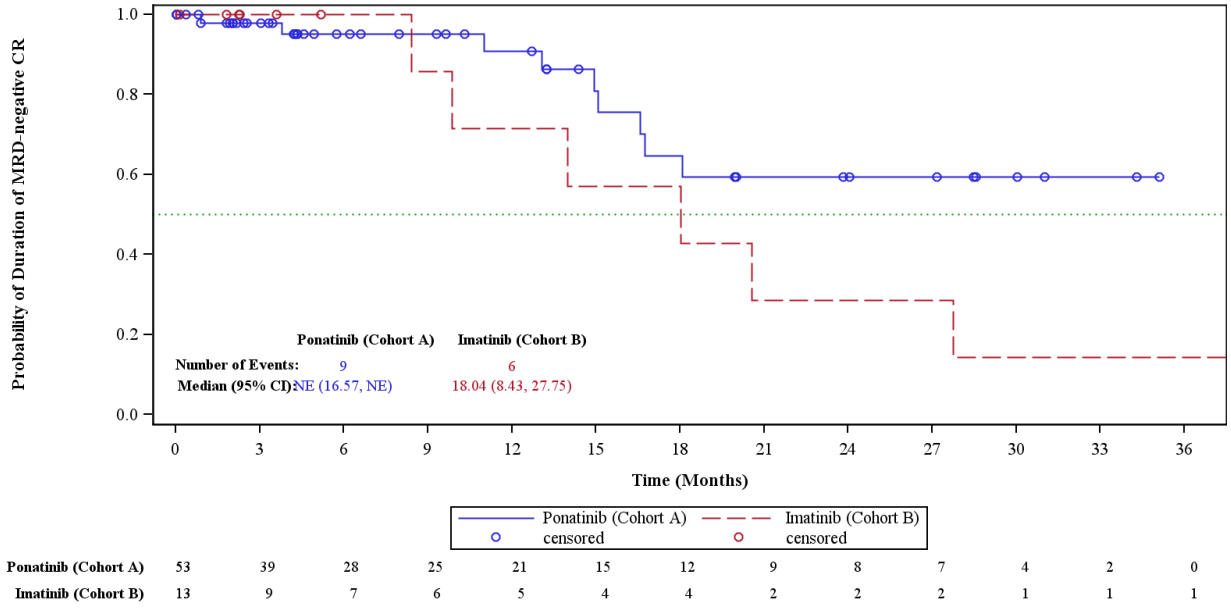
Note 1: Percentages are based on the number of participants within the category indicated.
Note 2: Rates are reported per the Protocol window of ± 7 days from time point.
[a] Minimal residual disease-negative CR rate is defined as the proportion of participants who achieved MRD-negative CR (≤ 0.01% BCR-ABL1/ABL1 or undetectable BCR-ABL1 transcripts in cDNA with ≥ 10,000 ABL1 transcripts, and meeting criteria for CR).
[b] The 95% confidence intervals were calculated using the exact binomial method.

Duration of MRD-Negative CR

At the time of the data cutoff, participants in the ponatinib arm had a longer duration of MRD-negative CR after induction compared to those in the imatinib arm. Among participants in the ITT population with p190/p210 variant who achieved MRD-negative CR at the EOI, the proportion of participants who lost MRD-negative status after induction was similar in the ponatinib (11.3%) and imatinib (7.7%) arms, and the proportion of participants who relapsed from CR was substantially lower in the ponatinib arm (5.7%) compared to the imatinib arm (38.5%).

Median time to loss of MRD-negative CR was not reached in the ponatinib arm and was 18.04 months (95% CI: 8.43, 27.75) in the imatinib arm. The KM estimated proportion of participants who maintained MRD-negative CR status at 9 months was higher in the ponatinib arm (95.2%; 95% CI: 81.9, 98.8; n = 25) compared to the imatinib arm (85.7%; 95% CI: 33.4, 97.9; n = 6).

Figure 9: Kaplan-Meier Plot for Duration of MRD-Negative CR (ITT Population with p190/p210 Variant Who Achieved MRD-Negative CR at the End of Induction)



Source: Ponatinib-3001 CSR Figure 15.2.1.4.

Molecular Response Rates (MR3, MRD Negativity [MR4 or Better], and MR4.5) at Multiple Intervals

Molecular Response at the End of Induction

Rates of MRD negativity, defined as BCR-ABL1/ABL1 levels ≤ 0.01% (MR4) at the EOI, were higher for participants in the ponatinib arm (43.0%) compared to those in the imatinib arm (22.1%). A deep molecular response, defined as BCR-ABL1/ABL1 levels ≤ 0.0032% (MR4.5), was reported for a higher proportion of participants in the ponatinib arm (26.8%) than in the imatinib arm (14.7%).

MR2 rate is defined BCR-ABL1/ABL1≤ 1% and MR3 rate is BCR-ABL1/ABL1 ≤ 0.1%.

Table 17: Study Ponatinib-3001 Summary of Molecular Response Assessment at the End of Induction (Cycle 3) by Treatment Arm (ITT Population With a p190 or p210 Variant)

	Ponatinib Arm (Cohort A) N = 154	**Imatinib Arm (Cohort B) N = 78**
At the end of Cycle 3, Induction Phase		
BCR-ABL1/ABL1 Ratio n (%)		
n[a]	142	68
> 1%	4 (2.8)	9 (13.2)
≤ 1% (MR2)	138 (97.2)	59 (86.8)
≤ 0.1% (MR3)	102 (71.8)	37 (54.4)
≤ 0.01% (MR4)	61 (43.0)	15 (22.1)
≤ 0.0032% (MR4.5)	38 (26.8)	10 (14.7)
EOT/ET[b]	6	8

	Ponatinib Arm (Cohort A) N = 154	Imatinib Arm (Cohort B) N = 78
Not evaluable	5	2
MR4 at baseline[c]	1	0
MR3 rate (95% CI)[d]	71.8 (63.7, 79.1)	54.4 (41.9, 66.5)
Relative risk (95% CI)[e]	1.32 (1.04, 1.68)	—
Risk difference (95% CI)	0.17 (0.03, 0.32)	—
MR4 rate (95% CI)[d]	43.0 (34.7, 51.5)	22.1 (12.9, 33.8)
Relative risk (95% CI)[e]	1.94 (1.19, 3.17)	—
Risk difference (95% CI)	0.21 (0.08, 0.34)	—
MR4.5 Rate (95% CI)[d]	26.8 (19.7, 34.8)	14.7 (7.3, 25.4)
Relative risk (95% CI)[e]	1.81 (0.96, 3.43)	—
Risk difference (95% CI)	0.12 (0.01, 0.23)	—

Note 1: MR2 rate is defined as the proportion of participants who achieved molecular response 2-log reduction (BCR-ABL1/ABL1≤ 1%, with ABL1 ≥ 100 copies).
Note 2: MR3 rate is defined as the proportion of participants who achieved molecular response 3-log reduction (BCR-ABL1/ABL1 ≤ 0.1%, with ABL1 ≥ 1000 copies).
Note 3: MR4 rate is defined as the proportion of participants who achieved molecular response 4-log reduction (BCR-ABL1/ABL1 ≤ 0.01%, with ABL1 ≥ 10,000 copies).
Note 4: MR4.5 rate is defined as the proportion of participants who achieved molecular response 4.5-log reduction (BCR-ABL1/ABL1 ≤ 0.0032%, with ABL1 ≥ 32,000 copies).
Note 5: Participants with p190/p210 variants are identified by central lab.
Note 6: Rates are reported per the Protocol window of ± 7 days from time point.
Note 7: Percentages are calculated out of the total number of participants with evaluable MRD status. Does not include 1 participant with MR4 at baseline.
[a] n was used as the denominator for this section.
[b] End of treatment/early termination = discontinued treatment/early termination before the EOI.
[c] Participants with BCR-ABL1/ABL1 > 0.01% at screening but ≤ 0.01% at Cycle 1 Day 1.
[d] The 95% CIs were calculated using the exact binomial method.
[e] The stratified CMH method was used to estimate the odds ratio with its 2-sided 95% CI and p-value. The stratification factors included the randomization strata (age): 18 through < 45 years, ≥ 45 through < 60 years, and ≥ 60 years.

Molecular Response at Additional Time Points

Higher rates of MRD negativity (defined as MR4 or better) and deep molecular response (defined as MR4.5) were achieved at earlier time points throughout the study for participants in the ponatinib arm compared with those in the imatinib arm. At the end of Cycle 3, higher rates of MR4 (ponatinib: 43.0%, imatinib: 22.1%) and MR4.5 (ponatinib: 26.8%, imatinib: 14.7%) were observed in the ponatinib arm. At the end of consolidation (Cycle 9), MR4 (ponatinib: 91.7%, imatinib: 46.7%) and MR4.5 (ponatinib: 62.5%, imatinib: 26.7%) rates remained higher in the ponatinib arm.

Duration of MR4 and MR4.5

Duration of MR4

Duration of MRD negativity was defined as participants with a p190 or p210 variant as assessed by the central laboratory who achieved at least MR4 response at the EOI. At the time of the data cutoff, a lower proportion of participants in the ponatinib arm (12.9%) had loss of MRD negativity compared to the imatinib arm (20.0%). Median time to loss of MRD negativity was not reached in the ponatinib arm but was reached in the imatinib arm at 20.89 months (95% CI: 10.86, NE).

Duration of MR4.5

Among participants who achieved a deep molecular response of MR4.5 at the EOI (participants with a p190 or p210 variant as assessed by the central laboratory) at the time of the data cutoff, 6 (15.4%) participants and 2 (20.0%) participants had loss of MR4.5 response in the ponatinib and imatinib arms, respectively. Median time to loss of deep molecular response was not reached in the ponatinib arm but was reached in the imatinib arm at 25.57 months (95% CI: 10.79, NE).

CR and CRi at Multiple Intervals

CR and CRi at the End of Induction

Similar CR or CRi rates at the EOI were observed for participants in the ponatinib (87.8%) and imatinib (87.7%) arms. A slightly higher rate of CR at the EOI was observed in the ponatinib arm (86.0%) compared to the imatinib arm (79.0%). A slightly lower rate of CRi was observed in the ponatinib arm (1.8%) compared to the imatinib arm (8.7%) at the EOI.

CR and CRi by or at the End of a Treatment Cycle After the End of Induction

Similar noncumulative CR or CRi rates that were achieved or maintained at the end of each cycle throughout the study were observed for participants in the ponatinib and imatinib arms. A higher rate of CR was observed in the ponatinib arm compared to the imatinib arm at the end of Cycle 3 and Cycle 9. A lower rate of CRi was observed in the ponatinib arm compared to the imatinib arm at the end of Cycle 3 (ponatinib: 2.1%, imatinib: 9.9%) and Cycle 9 (ponatinib: 3.6%, imatinib: 25.0%).

Similar cumulative CR or CRi rates, achieved any time before or at the specified time point, were observed by the end of each cycle throughout the study after Cycle 3 for participants in the ponatinib and imatinib arms. Similar CR rates were observed throughout the study for participants in the ponatinib and imatinib arms.

Primary Induction Failure

The rate of PIF, defined as participants who did not achieve CR or CRi by the EOI (end of Cycle 3), was similar among participants in the ponatinib arm (6.1% [95% CI: 3.0, 10.9]) compared to those in the imatinib arm (2.5% [95% CI: 0.3, 8.6].

PFS

A post hoc analysis of PFS was conducted using the EFS criteria (ie, death due to any cause, failure to achieve CR by the EOI, and relapse from CR) with the addition of 1 criterion: failure to achieve MRD negativity by the EOT or loss of MRD negativity.

MRD assessment has been adopted universally by physicians and is used broadly in current practice for monitoring disease response and determining treatment strategies for participants with Ph+ ALL. These treatment strategies may include continuing treatment with chemotherapy in combination with a TKI, undergoing HSCT followed by maintenance therapy with a TKI, or switching to an alternative therapy (NCCN 2024, Short et al 2019). In addition, physicians often regard the loss of MRD negativity or persistent MRD positivity as progressive disease and thus switch a participant to a subsequent therapy or perform HSCT while the participant is in CR but remains MRD positive. Therefore, PFS was analyzed for Study Ponatinib-3001 to reflect the current clinical practice when treating participants with Ph+ ALL.

At the time of the FA for the primary endpoint, there were 77 (47.0%) events in the ponatinib arm and 54 (66.7%) events in the imatinib arm. Median follow-up period on study for PFS was 20.68 months

(95% CI: 17.32, 24.29) in the ponatinib arm and 19.18 months (95% CI: 14.32, 30.54) in the imatinib arm. A 41.8% reduction in the risk of experiencing a PFS event was reported in the ponatinib arm compared to the imatinib arm with an HR of 0.582 (95% CI: 0.410, 0.827).

Ponatinib in combination with chemotherapy demonstrated median PFS with an increase of 12 months for the ponatinib arm compared to the imatinib arm (19.96 months [95% CI: 11.79, NE] vs 7.86 months [95% CI: 6.21, 12.39]).

Exploratory Endpoints

Time to HSCT

At the time of the data cutoff, the proportion of participants with HSCT events was higher in the imatinib arm (48.1%) compared to the ponatinib arm (34.1%). Median time to HSCT was not reached in the ponatinib arm and was 11.57 months (95% CI: 8.61, 24.79) in the imatinib arm.

Time to Subsequent Antineoplastic Therapy

At the time of the data cutoff, participants in the ponatinib arm exhibited a trend toward longer time to subsequent antineoplastic therapy compared to those in the imatinib arm. The proportion of participants with subsequent antineoplastic therapy events was lower in the ponatinib arm (34.8%) compared to the imatinib arm (56.8%). Median time to subsequent antineoplastic therapy appeared substantially longer in the ponatinib arm by nearly 22 months (32.39 months [95% CI: 20.32, NE]) compared to the imatinib arm (10.96 months [95% CI: 7.32, 14.57]).

Table 18: Subsequent Anticancer Therapy by Treatment Arm Safety Population

Anticancer Therapy	Ponatinib Arm (Cohort A) (N=163) n (%)	Imatinib Arm (Cohort B) (N=81) n (%)	Total (N=244) n (%)
Subjects with Any Subsequent Anticancer Therapy	57 (35.0)	46 (56.8)	103 (42.2)
Dasatinib	17 (10.4)	24 (29.6)	41 (16.8)
Ponatinib	13 (8.0)	12 (14.8)	25 (10.2)
Imatinib	17 (10.4)	7 (8.6)	24 (9.8)
Blinatumomab	12 (7.4)	10 (12.3)	22 (9.0)
Nilotinib	2 (1.2)	6 (7.4)	8 (3.3)
Transplant Conditioning procedure*	1 (0.6)	3 (3.7)	4 (1.6)
HSCT*	0	2 (2.5)	2 (0.8)
Investigational study	0	2 (2.5)	2 (0.8)
Blinatumomab + ponatinib	0	1 (1.2)	1 (0.4)
Subjects with at least one chemotherapy agent	30 (18.4)	25 (30.9)	55 (22.5)

Note: Chemotherapy included a variety of anticancer agents.
Note: * Data for these patients was recorded on subsequent treatment page and other patients have data reported on stem cell transplant page, see Listing 16.2.4.6.

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 19. Summary of Efficacy for trial Ponatinib-3001

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

Study identifier	www.clinicaltrials.gov EudraCT Number: 2018-000397-30		
Design	Randomized, open-label, multicenter		
	Duration of Main phase: Duration of Run-in phase: Duration of Extension phase:		Twenty 28-day cycles of TKI + reduced intensity chemotherapy Not applicable TKI continued until end of study
Hypothesis	Superiority		
Treatments group	ponatinib + chemotherapy imatinib + chemotherapy		Three 28-day cycles of TKI + Vincristine + Dexamethasone (induction) Six 28-day cycles of TKI + Methotrexate + Cytarabine (consolidation) Eleven 28-day cycles of TKI + Vincristine + Prednisone (maintenance) TKI continued until end of study N = 245
Endpoints and definitions	Primary:	MRD-negative CR	MRD-negative CR at the end of induction
	Secondary:	EFS	EFS, defined as the date of randomization until: – Death due to any cause. – Failure to achieve CR by the end of induction. – Relapse from CR
Database lock	Data cut-off 12 August 2022		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	All randomized patients who were identified by the central laboratory as having a baseline BCR-ABL1 dominant variant of p190 or p210. N=232		
Descriptive statistics and estimate variability	Treatment group	ponatinib + chemotherapy	imatinib + chemotherapy
	Number of subjects	154	78
	MRD-negative CR (%)	34.4%	16.7%
	Risk difference (95% CI)	0.18 (0.06, 0.29)	
	p-value	0.0021	
Analysis description	**Secondary analysis** EFS was not formally tested since as the prespecified number of events (130) had not been reached.		
Descriptive statistics and estimate variability	Treatment group	ponatinib + chemotherapy	imatinib + chemotherapy
	Number of subjects	164	81
	Patients with event (%)	34 (20.7%)	24 (29.6%)
	Median EFS time, months (95% CI)	NE (NE, NE)	29.0 (22.3, NE)
	Hazard Ratio (95% CI)	0.652 (0.385, 1.104)	

Supportive studies

Study AP24534-11-001 – Phase 2 study of combination of hyper-CVAD and ponatinib in patients with Philadelphia (Ph) chromosome positive and/or BCR-ABL positive acute lymphoblastic leukemia (ALL)

This was an investigator-sponsored study conducted at MD Anderson Cancer Center (MDACC) in Houston, Texas in collaboration with ARIAD Pharmaceuticals, Inc (a wholly owned subsidiary of Takeda Pharmaceutical Ltd. Co.). All study assessments were performed at MDACC. The study was monitored by MDACC.

It was a single-center, single-arm, phase 2 trial to evaluate the long-term efficacy and safety of ponatinib in combination with chemotherapy in newly diagnosed Ph+ ALL.

Objectives

The primary objective of this study was to evaluate the clinical efficacy (EFS) of an intensive short-term chemotherapy regimen (hyper CVAD program) given in combination with the TKI ponatinib for

Ph+ and/or BCR ABL1-positive ALL. The secondary objectives were to evaluate other clinical efficacy endpoints (ORR and OS) and safety of the regimen.

Design

This is a single-center, single-arm, Phase 2 study to evaluate the long-term efficacy and safety of ponatinib in combination with chemotherapy in Ph+ ALL, with participants continuing in follow-up. Eligible participants had newly diagnosed Ph+ ALL that was either previously untreated or previously treated with 1 to 2 cycles of chemotherapy with or without other TKIs.

Inclusion/Exclusion Criteria

Participants were eligible for inclusion if they were ≥ 18 years old and had a diagnosis of Ph+ ALL or lymphoid AP or BP CML that was either previously untreated or had been treated with 1 to 2 courses of chemotherapy with or without other TKIs. Participants were also required to have ECOG performance status ≤ 2 and adequate hepatic, pancreatic, and cardiac function.

Participant Enrolment

This open-label Phse 2 study enrolled participants starting 17 NOV 2011. At the time of the data cutoff (14 DEC 2020), there were no participants on study treatment and 45 participants (51.7%) remained in the long-term follow-up phase.

Data are presented from study initiation until the data cutoff date of 14 DEC 2020. At the time of the data cutoff, the median duration of follow-up for OS of all enrolled participants was 45.1 months (95% CI: 36.50, 63.10). There were 87 participants in the enrolled (safety) population.

Study Population Results

Disposition

As of the data cutoff, 42 participants (48.3%) discontinued treatment; 11 (26.2%) were discontinued after completing the study per Protocol. The reason "other" was reported in 10 participants (23.8%) and included SCT (n = 2) and moving to an umbrella, long term follow-up study for participants completing therapy on Department of Leukemia Protocols (n = 8). Other reasons for discontinuation included death (10/87, 23.8%), withdrawal by investigator or participant, lost to follow-up, and toxicity/side effects/complications.

Demographics and Baseline Characteristics

The median age was 46.0 years (range: 21-80 years); 50.6% of participants were male and 73.6% were White. At baseline, most participants (62.1%) had an ECOG score of 1. Six participants (6.9%) had CNS disease and 75.9% were not CD20 positive. Most participants (72.4%) had the p190 BCR ABL1 transcript and had a cytogenetic abnormality of the Ph+ chromosome (77.0%). Of the 87 participants in the study, 67 participants had Ph+ ALL.

Prior Treatments

Twenty-one participants had prior lines of therapy. Of these participants, 16 entered the study with CML (AP or BP); prior lines of therapy for these participants included 12 participants who received chemotherapy in combination with TKIs (dasatinib or imatinib) and/or rituximab, 1 participant who received chemotherapy alone, 1 participant who received imatinib and steroids, and 1 participant who received dexamethasone and dasatinib. Of the participants with Ph+ ALL, 5 participants received prior treatment; 2 participants received chemotherapy alone and 3 participants received chemotherapy in combination with TKIs (dasatinib or imatinib).

Efficacy Results

Primary Efficacy Endpoint

The primary endpoint in this study was EFS at 24 months in the safety population. Event-free survival was defined as the time from the first day of treatment until any failure resistant disease, relapse, or death, whichever occurred first. The KM estimated EFS rate was 75.1% at 2 years. Twenty-six participants (29.9%) had events during the study.

Study INCB 84344-201 (monotherapy ponatinib): Front-line treatment of Philadelphia positive (Ph+)/ BCR-ABL positive acute lymphoblastic leukemia (ALL) with ponatinib (INCB084344), a new potent tyrosine kinase inhibitor (TKI). A phase II exploratory multicentric study in patients more than 60 years old or unfit for a program of intensive chemotherapy and stem cell transplantation.

Data from the INCB 84344 201 CSR (cutoff date 24 APR 2020) and the INCB 84344 201 CSR Addendum 1 (cutoff date 30 SEP 2021) are summarized here.

Objectives

The primary objective of this completed study was to evaluate the therapeutic effects of ponatinib (CHR at 6 months) in participants with Ph+ ALL who were ≥ 60 years old or ≥ 18 years old and unfit for chemotherapy and SCT. Patients in this population already have a rate of CHR that is close to 100% with other TKIs but the relapse rate at 1 year is 50% or more; therefore, the purpose of this study was to induce better and longer remissions.

Key secondary objectives included evaluation of CHR and CCyR at 6, 12, 24, 36, and 48 weeks; duration of CCyR; CMR and MMR at 12, 24, 36, and 48 weeks; and duration of CMR. Event free survival and OS were also assessed.

Design

This was a multicenter, Phase 2, single-arm unblinded study of oral ponatinib in patients with Ph+ ALL. Patients ≥ 60 years old or ≥ 18 years old and unfit for a program of intensive chemotherapy and SCT were included. The study core phase comprised steroid pretreatment for 7 to 14 days, followed by ponatinib treatment for 48 weeks combined with steroid treatment for the first 29 days and intrathecal therapy every 28 days.

Inclusion/Exclusion Criteria

Male and female patients, ≥ 60 years old or ≥ 18 years old and unfit for intensive therapy program and allogeneic SCT, with Ph+ ALL (with more than 20% blasts in BM at diagnosis and no prior history of CML) were enrolled in this study.

Participant Enrollment

This study enrolled participants from 04 DEC 2014 to 24 JAN 2017. Data are presented from the date the first participant enrolled (04 DEC 2014) to a data cutoff date of 24 APR 2020.

The study was conducted at 23 study centers in Italy. A total of 44 participants were enrolled at 22 study centers.

Study Population Results

The data collected at baseline, including the derived baseline values for disposition, demographics, and baseline characteristics, use a 30 SEP 2021 data cutoff date to include assessments completed on Day 1 that were missing from the primary analysis (24 APR 2020 cutoff date). The updated baseline values are fully aligned with the definition in the SAP and remain consistent with the primary CSR.

Disposition

All 44 participants (100.0%) received at least 1 dose of study drug. A total of 27 participants (61.4%) completed the core phase of the study and 17 participants (38.6%) discontinued treatment during the core phase. The reasons for treatment discontinuation in the core phase were excess toxicity (including myelotoxicity, organ failure, and toxic death) in 6 participants (13.6%), physician decision in 6 participants (13.6%), documented hematologic or extramedullary relapse in 3 participants (6.8%), death in 1 participant (2.3%), and cytogenetic relapse in 1 participant (2.3%).

After the core phase, a total of 27 (61.4%) participants entered the extension phase of the study and continued to receive study treatment. At the initial data cutoff date of 24 APR 2020, 17 participants had discontinued from the extension phase and 10 participants remained in the extension phase and were ongoing on treatment beyond 24 months. As of the final data cutoff date of 30 SEP 2021, all 27 participants who entered the extension phase had discontinued study treatment.

Demographics and Baseline Characteristics

The median age was 66.5 years (range: 26-85 years) and 35 participants were aged ≥ 60 years. Overall, 50.0% of participants were male.

The median time since diagnosis of ALL was 13.5 days (range 5-66 days). Most participants had an ECOG score of 0 (40.9%) or 1 (38.6%). There were no participants with recorded baseline ECOG scores ≥ 3.

Bone marrow hypercellularity was reported in 26 participants (59.1%), hypocellularity was reported in 8 participants (18.2%), and normal cellularity was reported in 7 participants (15.9%); data were missing for 3 participants (6.8%). Disease in the CNS was reported for 6 participants (13.6%); 36 participants (81.8%) did not have CNS disease and data were missing for 2 participants (4.5%).

The majority of participants had BCR ABL transcripts in the BM, with the p190 transcript detected in 29 participants (65.9%), the p210 transcript detected in 7 participants (15.9%), and both the p190 and p210 transcripts detected in 4 participants (9.1%); data were missing for 4 participants (9.1%).

Prior Treatments

All participants in this study were previously untreated for Ph+ ALL. A run-in course of prednisone was administered to all participants for 7 to 14 days before ponatinib.

Efficacy Results

Primary Efficacy Endpoint

At 6 months of treatment, 86.4% (38 of 44) of participants were in CHR.

Other Efficacy Endpoints:

- Hematologic response:
  - The proportion of participants in CHR was 90.9% at Week 6, 84.1% at Week 12, 86.4% at Week 24, 65.9% at Week 36, and 56.8% at Week 48.
  - 42 participants achieved CHR at any time during treatment.
  - At the final data cutoff date of 30 SEP 2021, 9 participants remaining in CHR continued to receive ponatinib treatment.
- Cytogenetic response:

- The proportion of participants in CCyR was 47.7% at Week 6, 43.2% at Week 12, 54.5% at Week 24, 36.4% at Week 36, and 34.1% at Week 48.
- 34 participants achieved CCyR at any time during treatment.

- Molecular response:
  - The proportion of participants in CMR was 47.7% at Week 6, 47.7% at Week 12, 40.9% at Week 24, 40.9% at Week 36, and 36.4% at Week 48.
  - 36 participants achieved CMR at any time during treatment.
  - The proportion of participants in MMR was 34.1% at Week 6, 25.0% at Week 12, 31.8% at Week 24, 18.2% at Week 36, and 13.6% at Week 48).
- EFS and OS:
  - The median EFS was 29.54 months (95% CI: 18.27, 60.32), and the median OS was 61.67 months (95% CI: 25.82, NE) at the final data cutoff date of 30 SEP 2021.

2.4.3. Discussion on clinical efficacy

The MAH is applying for an approval of ponatinib in combination with reduced-intensity chemotherapy for the first line treatment of Ph+ ALL.

Design and conduct of clinical studies

The pivotal study supporting the sought indication is the ongoing study Ponatinib-3001 (PhALLCON). This phase 3, randomized, open-label, multicenter study is comparing ponatinib versus imatinib, administered in combination with reduced-intensity chemotherapy, in patients with newly diagnosed Ph+ ALL.

Dose response studies

The presently approved starting dose of ponatinib is 45 mg once daily, for Ph+ ALL previously treated with other TKIs or who have the T315I mutation. In the current application, the MAH suggests a lower starting dose of 30 mg once daily based on the PhALLCON study.

In the two supportive studies (AP 24532-11-001 and INCB 84344-201) 45 mg ponatinib once daily was investigated. The choice of this dose was based on earlier phase 1-2 trials that indicated that a dose-effect relationship exists with the occurrence of responses and the MTD defined in the phase 1 trial AP24534-07-101. No formal dose-response studies were carried out for the applied 1L Ph+ ALL indication.

However, logistic regression analyses of dose intensity-AE relationships in participants with CP CML in the phase 2 Study AP24534-10-201 indicated a dose-dependent increase in AEs, including arterial occlusive events. This led to the expectation that the ponatinib 30 mg QD dose will have a better safety profile in combination with reduced-intensity chemotherapy compared with 45 mg QD; thus, supporting the selection of the 30 mg QD starting dose for evaluation in Study Ponatinib-3001. In this study, the exposure-efficacy analysis showed that ponatinib exposure was not a statistically significant predictor of MRD-negative CR at the EOI.

The rationale for the starting dose provided by the MAH is acknowledged.

Study participants

Eligible patients were aged ≥ 18 years and had newly diagnosed Ph+ ALL. Patients with a history or current diagnosis of CML; those with prior or current treatment with any systemic anticancer therapy and/or radiotherapy for ALL; and those with clinically significant, uncontrolled, or active cardiovascular, cerebrovascular, or peripheral vascular disease, or history of or active venous thromboembolic events disease or with clinically relevant CNS pathology were excluded from the study.

Treatments

Participants were randomized in a 2:1 ratio to receive ponatinib (ponatinib arm) or imatinib (imatinib arm) QD. Both TKIs were administered in combination with reduced intensity chemotherapy for 3 cycles of induction therapy, 6 cycles of consolidation therapy, and 11 cycles of maintenance therapy, followed by treatment with single-agent ponatinib or imatinib administered continuously after Cycle 20.

ESMO interim update GL 2023 recommends reduced intensity chemotherapy and a first- or second generation TKI followed by allo-HSCT as the standard therapy for newly diagnosed patients.

Participants randomized to the ponatinib arm received a starting dose of 30 mg ponatinib QD, with a dose reduction to 15 mg QD if they achieved MRD negative CR by the EOI (end of Cycle 3) or later. If a participant had a loss of MRD negativity after a per-Protocol dose reduction to 15 mg, dose re-escalation could be considered.

Participants randomized to the imatinib arm received 600 mg of imatinib QD. A cycle of therapy comprised 28 days of treatment.

Endpoints

The primary endpoint was MRD-negative CR at the end of induction therapy. The key secondary endpoint was EFS, defined as the date of randomization until death due to any cause; failure to achieve CR by the end of induction or relapse from CR.

Recruitment and conduct of the study

The protocol was amended 6 times. In amendment 8, the definition of EFS was updated: "Updated the definition for EFS so that one of the events for EFS is based on failure to achieve CR by the end of induction instead of failure to achieve MRD-negative CR by the end of induction." The result of the analysis of EFS applying the definition before amendment 8 yields consistent results the one presented in the SmPC section 5.1.

As of the data cutoff, a total of 32 patients had at least 1 significant protocol deviation identified. The proportion of patients with at least 1 protocol deviation was similar in the ponatinib arm (13.5%) and the imatinib arm (12.3%). The analysis of the primary endpoint in a population with at least 1 significant Protocol deviation in participants with p190/p210 variant shows that protocol deviations had no impact on the FA of efficacy in this study.

Sample size

The sample size of 230 patients was initially planned but has been changed during the study. Prior to the interim analysis of the primary endpoint, the planned sample size was decreased to 150 patients (protocol amendment 8), then increased again to 230 patients (protocol amendment 10). The anticipated efficacy estimate varied in the sample size calculations; from the initial 28% difference in MRD-negative rates to a range of 20% to 28% in the final calculation.

Prior to the final analysis, the sample size was increased to 230 patients according to amendment 10. The MAH has clarified that according to the protocol amendment 8, the FA of MRD-negative CR was to be based on approximately 150 participants while EFS was to be tested after the accrual target of 230

participants accumulated 173 events. Hence, the targeted study sample size has already been 230 patients. A decision (in amendment 10) was to include all enrolled patients into the FA of MRD-negative CR, since the primary endpoint was not statistically significant at the interim analysis.

Statistical analysis

The study Ponatinib-3001 is open-label and subject to numerous protocol amendments including changes in the design and sample size for the primary endpoint. At the time of the data cutoff for the interim analysis, there was no statistical analysis plan written, and the effective protocol version was the protocol amendment 8 (dated 10 February 2021). The significance boundary for MRD-negative CR was not achieved by the data cutoff for the interim analysis.

The first version of the SAP was authored shortly after the data cutoff for the interim analysis, and the date of the interim database lock could not be found, therefore it cannot be excluded that the SAP was influenced by the data at hand as the study was open label.

While the protocol amendment 8 stipulated that the efficacy analysis was to be performed on the ITT population, the SAP defined the primary population as a subset of ITT, and in a slightly different descriptions in version 1 and the final SAP version. As of the final SAP, the primary analysis was performed based on the ITT who have been identified with BCR-ABL1 dominant variants of p190 or p210. Of note, the MRD status (i.e., negativity) was measured separately from the testing of p210 and p190 variants. This makes the modified ITT definition a post-hoc decision.

Considering that the study was open-label and that the primary analysis population was changed from ITT to a subset of ITT late during the study conduct, and also considering that the MRD status was measured separately from testing of p210 and p190 variants, use of the modified primary population "ITT who have been identified with BCR-ABL1 dominant variants of p190 or p210" raised questions. The MAH explained the modification of the MRD primary analysis population by the fact that the central laboratory could not confirm a p190 or p210 variant for all randomized participants at the time for protocol revision 10. The primary analysis was provided based on the ITT population (imputing missing data as failures) which confirmed the MRD-negative CR results in the ITT population with p190/p210 variant. The ITT analysis was reassuring for robustness of the MRD-negative CR results.

The primary analysis for MRD-negative CR was to be conducted using a Cochran-Mantel-Haenszel (CMH) chi-square test, with no details on stratification provided in the SAP. However, the results are presented using the CMH test stratified by randomization strata. Although it is supported to stratify the primary analysis according to the randomisation stratification, the MAH has also presented unstratified CMH analysis based on the ITT population, and based on the ITT who have been identified with BCR-ABL1 dominant variants of p190 or p210. The results are similar to the results of the corresponding stratified analyses.

The MRD-negative CR rate was tested at the IA and the FA at the significance level determined by the O'Brien-Fleming alpha spending function (the Lan-DeMets method) using the group sequential testing approach. An interim analysis for the MRD-negative CR primary endpoint was performed at the data cutoff 17 February 2021. The valid protocol version at that timepoint was the protocol amendment 8, which stated that an efficacy boundary of 0.021 was to be used at the interim analysis based on data from 115 patients. The actual IA for MRD-negative CR used efficacy boundary of 2-sided 0.022 given that 116 patients had been observed. At the FA, an efficacy boundary was 2-sided 0.036 if the number of patients was 230. However, an FA for approximately 150 patients would have used a 2-sided efficacy boundary of 0.043 (per protocol amendment 8). The sensitivity analysis of the primary endpoint was performed based on the first 150 patients enrolled, and was statistically significant at this level.

The EFS was to be tested only if the primary endpoint comparison achieved statistical significance, as it did. The analysis of EFS was based on time-to-event analysis. One IA and one FA was planned for EFS at the significance level determined by the Gamma Family (-1) alpha spending function using the group sequential testing approach. At the IA for EFS, alpha spending is to equal 0.033 with an efficacy boundary of 0.033 for EFS if the observed number of events is 130; at the FA, alpha spending is to equal 0.017 with an efficacy boundary of 0.034 for EFS if the observed number of events is 173.

At the time of data cutoff, 58 EFS events were reported. Although the MAH states that EFS was not formally tested as the prespecified number of events for the interim analysis had not been reached, an analysis of EFS has been performed at the data cutoff resulting in HR and its 95% confidence interval that indicate a lack of statistical significance when comparing the treatment groups. In light of the reported EFS results, and the importance of EFS to support the efficacy conclusions, a concern was raised about the type I error control for EFS. The MAH was asked to clarify the alpha spent in the analysis based on 58 events, and how type I error will be controlled in the upcoming EFS analyses. The MAH responded that no claims were intended from EFS analysis at this time and explained that confidence intervals and tests were of descriptive nature. However, by performing a statistical test (even if other from the formally pre-specified test for testing EFS, i.e. log-rank), the MAH obtains valuable information before formal interim analysis. This raises a concern about the study integrity. Also, the unplanned analysis results in a loss of the type I error control even though no claims are intended at this time, since it was not prespecified how a positive result would have been used. Whether a p-value at the unplanned analysis was obtained from a prespecified log-rank test or not, becomes irrelevant as the hypothesis testing was unplanned. Further, performing unplanned testing in an open label study merely constitutes explorative research. This approach is therefore questionable. For the mentioned reasons, the type I error control for EFS is considered lost, which implies that only descriptive statistics and nominal p-values may be presented for EFS in the SmPC.

Considering the use of alpha spending function in the group sequential testing, the overall type I error rate for the primary endpoint was to be controlled at a 2-sided 0.05 alpha level, with the caveat of the open label nature of the study and the ongoing updates of the sample size.

Participant flow

A total of 339 patients were screened, whereof 85 were screen failures. (9 patients were screened in Japan. Patients enrolled in Japan were assigned to the ponatinib treatment arm and were not part of the ITT population.) The ITT population included a total of 245 patients, 164 patients were randomized to receive ponatinib 30 mg and 81 patients were randomized to receive imatinib.

Lost to follow up and withdrawal by patient was somewhat more frequent in the imatinib arm (lost to follow up: 0.0% in the ponatinib arm vs 1.2% in the imatinib arm; withdrawal by patient: 3.7% in the ponatinib arm vs 4.9% in the imatinib arm). This level of attrition does not raise concerns with respect to the robustness of outcomes.

Baseline characteristics

At baseline, the median age was 54 years (range: 19-82 years), most participants had an ECOG score of 0-1 and 54% were female. The majority of patients (68%) had the p190 BCR-ABL1 transcript. 10 (6.1%) patients in the ponatinib arm and 3 (3.7%) patients in the imatinib arm had atypical or undetermined/not tested BCR-ABL1 and were thus not included in the analysis for the primary endpoint. The presence of extramedullary disease was more frequent in the ponatinib arm (6.1% vs 3.7%)

Randomization was stratified dependent on age category: 18-<45, 45-<60 and ≥60 years. Stratification factors are endorsed.

46.9% of participants had received prephase anticancer therapy as permitted by the Protocol. Optional prephase therapy or chemotherapy induction (no more than 1 cycle) excluding TKI, was permitted by the Protocol. Duration of prephase therapy was similar between the 2 arms, median 8 (ponatinib arm) vs 7 (imatinib arm) days. Best prephase therapy response could not be assessed or was unknown in most patients.

Efficacy data and additional analyses

Primary endpoint

At the time of the final analysis for the primary endpoint, among the 232 participants in the ITT population with a baseline p190 or p210 variant, the MRD-negative CR rate at EOI for ponatinib (34.4%) was significantly higher compared to imatinib (16.7%) with a p-value of 0.0021. Thus, ponatinib as a first-line therapy, combined with reduced-intensity chemotherapy, achieved a statistically significant and improvement in MRD-negative CR rate at EOI in participants with newly diagnosed Ph+ ALL.

The presented subgroup results of the primary endpoint showed an overall consistent treatment effect.

Secondary endpoint

At the time of the data cutoff, EFS was not formally tested as the prespecified number of events (130) for analysis had not been reached. As of the data cutoff, 58 (44.6%) of the 130 required EFS events were reported. Median follow-up for EFS was 17 months in the ponatinib arm and 16 months in the imatinib arm.

Median EFS was not reached for the ponatinib arm and was 29.04 months (95% CI: 22.29, NE) for the imatinib arm. A 34.8% reduction in the risk of experiencing an EFS event was reported in the ponatinib arm with an HR of 0.652 (95% CI: 0.385, 1.104). The difference in EFS was not statistically significant.

The EFS KM curves separated around month 12 and stayed separated over time in favour of the ponatinib arm.

OS

OS results were immature at the time of analysis. There were 21 events (12.8%) in the ponatinib arm and 13 events (16.0%) in the imatinib arm. Although the OS trend favoured ponatinib (HR 0.761, 95% CI: 0.381, 1.520), the difference was not statistically significant. Median OS was not reached in either treatment arm. Importantly, the OS analysis was not adjusted for type I error.

Time to HSCT

Time to HSCT was an exploratory endpoint without type 1 error control. At the time of the data cutoff, the proportion of participants with HSCT events was higher in the imatinib arm (48.1%) compared to the ponatinib arm (34.1%). Median time to HSCT was not reached in the ponatinib arm and was 11.57 months (95% CI: 8.61, 24.79) in the imatinib arm.

It should be noted that the question whether knowledge of TKI allocation influenced HSCT decisions cannot be definitively answered within the present dataset. The fact that fewer patients in the ponatinib arm underwent HSCT does not, in itself, provide sufficient evidence to support the omission of HSCT in patients treated with ponatinib, since HSCT was not randomized and the decision to proceed with HSCT was made after the assessment of the primary end point in this open-label trial.

Supportive Studies

The results from both supportive studies (Study INCB 84344-201 and Study AP24534-11-001) demonstrate deep and durable molecular responses to ponatinib in combination with either steroids or high-intensity chemotherapy in participants with newly diagnosed Ph+ ALL.

In Study AP24534-11-001, high response rates were achieved with the combination of ponatinib with hyper-CVAD as evidenced by all participants reaching CR, 88.4% reporting MMR, and 78.3% reporting CMR. Evidence of durability of response was observed with stable EFS rates at 2, 3, and 5 years of 75.1%, 70.7%, and 68.1%, respectively. In addition, the OS rates at 1, 2, and 3 years were 88.2%, 81.5%, and 78.2%, respectively.

In Study INCB 84344-201, the efficacy and durability of outcomes of ponatinib in combination with steroid induction were observed in participants with Ph+ ALL aged 60 years and older, or aged 18 years and older and unfit for chemotherapy and SCT. At 6 months of treatment, 86.4% of participants were in CHR, 31.8% reported MMR, and 40.9% reported CMR. At the final data cutoff date, the median duration of CHR was 49.94 months (95% CI: 20.70, NE), median duration of CCyR was 36.70 months (95% CI: 21.91, NE), and median OS was 61.67 months (95% CI: 25.82, NE).

2.4.4. Conclusions on the clinical efficacy

Ponatinib as a first-line therapy, in combination with reduced-intensity chemotherapy, demonstrated a statistically significant improvement in the primary endpoint of MRD-negative CR rate at end of induction in participants with newly diagnosed Ph+ ALL. This is accompanied by a trend towards increased EFS. However, this is not nominally statistically significant.

The pivotal PhALLCON study has a substitution design where patients are randomised to standard of care imatinib or test agent ponatinib, as add-on to reduced intensity chemotherapy. Imatinib is approved for this use. This increases the rate of complete remissions and was shown to increase EFS and OS compared to chemotherapy alone, based on historical comparisons (Glivec SmPc, section 5.1.). Both imatinib and ponatinib provide antitumoral action by occupying the ATP-binding site of BCR-ABL1, thus sharing the same fundamental mechanism of action.

The increase in MRD-negativity with ponatinib demonstrates that this regimen provides more antitumoral activity than does imatinib. This indicates that, given a similar mechanism of action, and provided that it is sufficiently tolerated, the impact of ponatinib on EFS is likely to be at least similar to that of imatinib, and possibly greater.

MRD-negativity is presently not understood as a metric that independently isolates clinical benefit, and therefore is not an established registrational endpoint in this setting. Moreover, this has not been established as a trial-level surrogate of time to progression or overall survival.

However, in the context of a study where ponatinib is investigated as a substitute for imatinib (a product with established clinical benefit in the treatment context), a conclusion can be made that the efficacy of ponatinib is not inferior to that of imatinib. Further, the difference in MRD-negativity that was seen supports the hypothesis that ponatinib may provide longer EFS than imatinib. This is supported by available EFS data, although these in themselves are inconclusive at this time.

In summary, there is no concern that ponatinib would be less effective than the registered comparator, imatinib, and it may be superior. On this basis, an approval based on MRD-negativity is possible.

The following measures are considered necessary to address issues related to efficacy:

In order to confirm the efficacy and safety of Iclusig in combination with reduced-intensity chemotherapy in adult patients with newly diagnosed Ph+ ALL the MAH should submit the final results of Ponatinib-3001 (PhALLCON) a randomized, active controlled, multicenter, open label trial.

2.5. Clinical safety

Introduction

The safety data submitted in support of the current variation include:

(I) **Pivotal study:**

Study Ponatinib-3001 (PhALLCON), an ongoing, multicenter, open-label Phase 3 study of ponatinib + reduced intensity chemotherapy vs. imatinib + reduced intensity chemotherapy in patients with newly diagnosed Ph+ ALL.

(II) **Supportive studies:**

Study AP24534-11-001 (Study 001): An investigator-sponsored, single-centre, single-arm study of ponatinib as add-on to hyper CVAD in patients with newly diagnosed Ph+ ALL (n = 87)

Study INCB 84344 201 (Study 201): Exploratory single-arm study. Ponatinib monotherapy in patients with newly diagnosed Ph+ ALL, and that were ≥ 60 years old or ≥18 years old and unfit for chemotherapy and SCT (n= 44)

Ponatinib is previously indicated for adult patients

1. with chronic phase (CP), accelerated phase (AP), or blast phase (BP) 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
2. Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

Ponatinib is associated with **vascular occlusive events** (VOEs), including arterial occlusive events (AOEs) and venous thromboembolic events (VTEs). In the registrational study for ponatinib monotherapy in CML and Ph+ ALL, the PACE trial, overall arterial occlusive adverse reactions occurred in 25% of Iclusig-treated patients with a minimum 64 months follow-up, with serious adverse reactions occurring in 20% of patients. Some patients experienced more than one type of event. Venous thromboembolic reactions (treatment-emergent frequencies) occurred in 6% of patients. The incidence of thromboembolic events is higher in patients with Ph+ ALL or BP-CML than those with AP-CML or CP-CML. These effects have been shown to be dose dependent and therefore the approved SmPC includes a recommendation to consider a dose reduction from 45 mg to 15 mg once a CMR has been achieved. The recommendation was originally included following an Article 20 referral concerning the prothrombotic potential of ponatinib. The safety and efficacy of a range of starting doses and prospective dose reductions have been further evaluated within of Study AP24534-14-203 (OPTIC), the final results of which is currently discussed within the ongoing variation procedure EMA/VR/0000261199.

Ponatinib is associated with **myelosuppression**, which can be severe. In previous studies, the risk of myelosuppression was generally greater in patients with accelerated phase CML (AP-CML) or blast

phase CML (BP-CML)/Ph+ ALL than in chronic phase CML (CP-CML). The myelosuppression was generally reversible and usually managed by withholding ponatinib temporarily or reducing the dose. Infections are very commonly (upper respiratory tract infection) or commonly (pneumonia, sepsis, folliculitis, cellulitis) reported ADRs. Pneumonia was the most commonly reported serious infection. Febrile neutropenia was reported with frequency "Common".

Hepatotoxicity (hepatic failure) has been observed during treatment with ponatinib (uncommon). Increases in ALT and ALT were very common in the PACE study. Increases in blood bilirubin, ALP and GGT were common. The SmPC advices that liver function tests should be performed prior to treatment initiation and monitored periodically.

Cardiotoxic events have been reported, including cardiac failure and myocardial infarction (common) and left ventricular (LV) dysfunction (uncommon).

Dermatological reactions such as rash, pruritus, erythema and **gastrointestinal disorders** such as nausea, diarrhoea, vomiting, constipation are very commonly or commonly reported during treatment with ponatinib.

Pivotal study Ponatinib-3001 (PhALLCON)

Patient exposure

Patient exposure and duration of follow-up is shown in Table 20.

Patient disposition is shown in Table 21. In terms of patient disposition, the largest differences between treatment arms at the data cutoff were seen in proportion of subjects who were still on study treatment (41.5% and 12.3% in the ponatinib and imatinib arms, respectively), subjects ongoing on study but discontinued from study treatment (40.9% and 65.4%, respectively), subjects who discontinued due to lack of efficacy (7.3% and 25.9%, respectively) and subjects who had HSCT at any time (34.1 and 48.1%, respectively). There was no difference in the proportion of subjects who discontinued treatment due to an AE (12.2% and 12.3% in the ponatinib and imatinib arms, respectively).

Table 6. PhALLCON: Median duration of exposure and follow-up (data cut-off 12 august, 2022)

	Ponatinib	**Imatinib**
Median duration at final analysis of primary endpoint	7.3 months; range: <1 - 39 months	5.1 months; range: <1 - 41 months
Median number of treated cycles	7.0 (range: 1-39)	5.0 (range: 1-41)
Median relative dose intensity	100.0% (range: 81.9%-100.3%)	100.0% (range: 95.9% 106.5%)
Median duration of follow-up	20.43 months [95% CI: 18.39, 23.93]	18.14 months [95% CI: 13.86, 24.25]

Table 21. PhALLCON: Participant Disposition (ITT Population)

Categories	**Ponatinib Arm N = 164 n (%)**	**Imatinib Arm) N = 81 n (%)**	**Total N = 245 n (%)**
ITT population	164 (100)	81 (100)	245 (100)
ITT population with p190/p210 variant	154 (93.9)	78 (96.3)	232 (94.7)
Safety population	163 (99.4)	81 (100)	244 (99.6)
Perprotocol population	163 (99.4)	81 (100)	244 (99.6)

Categories	Ponatinib Arm N = 164 n (%)	Imatinib Arm) N = 81 n (%)	Total N = 245 n (%)
Participants randomized but not treated[a]	1 (0.6)	0	1 (0.4)
Participants randomized and treated	163 (99.4)	81 (100)	244 (99.6)
Participants discontinued from study	28 (17.1)	18 (22.2)	46 (18.8)
Participants ongoing on study	135 (82.3)	63 (77.8)	198 (80.8)
Participants ongoing on study treatment	68 (41.5)	10 (12.3)	78 (31.8)
Participants ongoing on study but discontinued from study treatment	67 (40.9)	53 (65.4)	120 (49.0)
Participants ongoing in followup[b]	61 (37.2)	44 (54.3)	105 (42.9)
Total participants discontinued from study treatment	95	70	165
Primary reason for study treatment discontinuation[c]			
HSCT	50 (30.5)	30 (37.0)	80 (32.7)
Adverse event	20 (12.2)	10 (12.3)	30 (12.2)
Protocol deviation	1 (0.6)	0	1 (0.4)
Lost to followup	0	0	0
Withdrawal by participant	5 (3.0)	1 (1.2)	6 (2.4)
Study terminated by sponsor	0	0	0
Progressive disease	7 (4.3)	5 (6.2)	12 (4.9)
Lack of efficacy	12 (7.3)	21 (25.9)	33 (13.5)
Relapse from CR	5 (3.0)	4 (4.9)	9 (3.7)
Failure to achieve CR	0	2 (2.5)	2 (0.8)
Failure to achieve MRD negativity[d]	7 (4.3)	15 (18.5)	22 (9.0)
Other	0	3 (3.7)	3 (1.2)
Total participants discontinued from study[a]	29[e]	18	47
Primary reason for study discontinuation[c]			
Death[a]	21 (12.8)	13 (16.0)	34 (13.9)
Lost to followup	0	1 (1.2)	1 (0.4)
Withdrawal by participant	6 (3.7)	4 (4.9)	10 (4.1)
Study terminated by sponsor	0	0	0
Other	2 (1.2)	0	2 (0.8)
HSCT at any time	56 (34.1)	39 (48.1)	95 (38.8)

Note 1: The ITT population is defined as all participants who were randomized. The ITT population with p190/p210 variant is defined as all participants in the ITT population who were identified by the central laboratory as having baseline BCR-ABL1 dominant variants of p190 or p210. The safety population is defined as all participants who were randomized to the ponatinib or imatinib arm and receive at least 1 dose of any study treatment. Percentages are calculated out of the number of participants randomized.

Note 2: Data cutoff date of 12 AUG 2022.

[a] One participant was randomized to ponatinib arm and died before receiving treatment.

[b] Participants who have had at least 1 followup visit recorded.

[c] From the "End of Treatment" CRF page.

[d] Failure to achieve MRD negativity is from local/investigator assessment.

[e] Includes participant who was randomized but not treated.

Adverse events

Treatment-emergent AEs (TEAEs) were defined as AEs that started or worsened in severity on or after the first dose of study treatment and no later than 30 days after the last dose.

MedDRA Version 25.0 was used for coding AEs.

An overview of treatment-emergent AEs (TEAEs) is shown in Table 22.

The largest difference between treatment groups was observed for the portion of subjects who had dose interruption due to a TEAE. According to the MAH, this difference is at least in part a result of dose modification guidelines that are more conservative in the Study Protocol and in the prescribing information for ponatinib than in the prescribing information for imatinib.

Table 22. Ponatinib-3001: Overview of Treatment-Emergent Adverse Events (Safety Population)

Variable	Ponatinib Arm N = 163 n (%)	Imatinib Arm N = 81 n (%)
Any TEAEs	162 (99.4)	80 (98.8)
Treatment-related TEAE	141 (86.5)	67 (82.7)
Serious TEAE	97 (59.5)	45 (55.6)
Serious treatment-related TEAE	34 (20.9)	16 (19.8)
Grade 1 TEAE	2 (1.2)	0
Grade 2 TEAE	13 (8.0)	5 (6.2)
Grade 3 TEAE	30 (18.4)	21 (25.9)
Grade 4 TEAE	109 (66.9)	50 (61.7)
Grade 5 TEAE[a]	8 (4.9)	4 (4.9)
Grade 3-4 TEAE	147 (90.2)	75 (92.6)
Grade 3-4 treatment-related TEAE	107 (65.6)	48 (59.3)
Grade 3-4 serious TEAE	85 (52.1)	37 (45.7)
Grade 3-4 serious treatment-related TEAE	30 (18.4)	15 (18.5)
TEAEs leading to treatment discontinuation, dose reduction, or dose interruption[b]	117 (71.8)	40 (49.4)
TEAEs leading to treatment discontinuation[c]	17 (10.4)	7 (8.6)
TEAEs leading to dose reduction	33 (20.2)	18 (22.2)
TEAEs leading to dose interruption	111 (68.1)	32 (39.5)
On-study deaths[d]	8 (4.9)	4 (4.9)

Note 1: Data cutoff date of 12 AUG 2022.
Note 2: TEAE is defined as any AE that occurs after administration of the first dose of any study treatment and through 30 days after the last dose of any study treatment.
Note 3: MedDRA Dictionary v25.0 was used for coding AEs.
Note 4: The counts for Grade 1 to 5 categories include participants who have highest grade in that category, and Grade 3-5 categories include participants whose highest grade is 3-5.
[a] All deaths reported in the AE domain within 30 days of last dose.
[b] A TEAE may be associated with more than 1 type of dose adjustment.
[c] All TEAEs with "Drug Withdrawn" as the action taken.
[d] All deaths reported in AE and disposition domain within 30 days of last dose.

Common adverse events

The most commonly reported TEAEs (≥ 10% in either treatment arm), are shown in Table 23.

Table 7. PhALLCON: Treatment-Emergent Adverse Events Occurring in ≥ 10% of Participants in Either Study Arm by System Organ Class and Preferred Term (Safety Population)

MedDRA SOC **MedDRA PT**	**Ponatinib Arm** **N = 163** **n (%)**	**Imatinib Arm** **N = 81** **n (%)**
Participants with at least 1 TEAE	162 (99.4)	80 (98.8)
Investigations	136 (83.4)	65 (80.2)
Alanine aminotransferase increased	68 (41.7)	27 (33.3)
Lipase increased	44 (27.0)	29 (35.8)
Platelet count decreased	39 (23.9)	26 (32.1)
Neutrophil count decreased	35 (21.5)	26 (32.1)
Aspartate aminotransferase increased	39 (23.9)	15 (18.5)
White blood cell count decreased	25 (15.3)	20 (24.7)
Gammaglutamyltransferase increased	21 (12.9)	8 (9.9)
Blood lactate dehydrogenase increased	19 (11.7)	8 (9.9)
Amylase increased	16 (9.8)	10 (12.3)
Gastrointestinal disorders	132 (81.0)	65 (80.2)
Nausea	57 (35.0)	41 (50.6)
Constipation	62 (38.0)	17 (21.0)
Vomiting	36 (22.1)	31 (38.3)
Diarrhoea	28 (17.2)	27 (33.3)
Stomatitis	31 (19.0)	16 (19.8)
Abdominal pain	26 (16.0)	10 (12.3)
Abdominal pain upper	23 (14.1)	6 (7.4)
Blood and lymphatic system disorders	125 (76.7)	64 (79.0)
Anaemia	72 (44.2)	44 (54.3)
Thrombocytopenia	77 (47.2)	31 (38.3)
Neutropenia	72 (44.2)	30 (37.0)
Febrile neutropenia	41 (25.2)	17 (21.0)
Leukopenia	23 (14.1)	12 (14.8)
Nervous system disorders	128 (78.5)	61 (75.3)
Headache	70 (42.9)	35 (43.2)
Neuropathy peripheral	51 (31.3)	19 (23.5)
Paraesthesia	33 (20.2)	8 (9.9)
Peripheral sensory neuropathy	18 (11.0)	10 (12.3)
Dizziness	16 (9.8)	10 (12.3)
General disorders and administration site conditions	113 (69.3)	57 (70.4)
Pyrexia	61 (37.4)	21 (25.9)
Fatigue	43 (26.4)	18 (22.2)

MedDRA SOC MedDRA PT	Ponatinib Arm N = 163 n (%)	Imatinib Arm N = 81 n (%)
Oedema peripheral	17 (10.4)	26 (32.1)
Asthenia	26 (16.0)	13 (16.0)
Face oedema	3 (1.8)	9 (11.1)
Metabolism and nutrition disorders	102 (62.6)	66 (81.5)
Hypokalaemia	40 (24.5)	31 (38.3)
Hyperglycaemia	27 (16.6)	15 (18.5)
Hypocalcaemia	22 (13.5)	18 (22.2)
Hypophosphataemia	17 (10.4)	17 (21.0)
Decreased appetite	15 (9.2)	15 (18.5)
Hyponatraemia	12 (7.4)	9 (11.1)
Hypoalbuminaemia	10 (6.1)	9 (11.1)
Infections and infestations	115 (70.6)	45 (55.6)
COVID-19	26 (16.0)	8 (9.9)
Musculoskeletal and connective tissue disorders	88 (54.0)	37 (45.7)
Back pain	31 (19.0)	11 (13.6)
Arthralgia	28 (17.2)	8 (9.9)
Pain in extremity	30 (18.4)	6 (7.4)
Myalgia	20 (12.3)	8 (9.9)
Muscular weakness	10 (6.1)	10 (12.3)
Skin and subcutaneous tissue disorders	83 (50.9)	32 (39.5)
Rash	31 (19.0)	13 (16.0)
Vascular disorders	75 (46.0)	22 (27.2)
Hypertension	52 (31.9)	11 (13.6)
Respiratory, thoracic, and mediastinal disorders	63 (38.7)	26 (32.1)
Cough	21 (12.9)	4 (4.9)
Psychiatric disorders	47 (28.8)	19 (23.5)
Insomnia	31 (19.0)	14 (17.3)

Note 1: TEAE is defined as any AE that occurs after administration of the first dose of any study treatment and through 30 days after the last dose of any study treatment.
Note 2: MedDRA Dictionary v25.0 was used for coding AEs.
Note 3: Participants with 1 or more AE within a level of MedDRA term is counted only once in that level.
Note 4: Data cutoff date of 12 AUG 2022.

Treatment-Related Adverse Events

TEAEs assessed as treatment-related occurred in a comparable proportion of participants in the treatment arms (Table 24).

Treatment-related TEAEs by PT that occurred in a larger proportion of participants (≥ 5% absolute difference) in the ponatinib arm compared to the imatinib arm were AST increased and hyperuricemia.

Treatment-related TEAEs by PT that occurred in a smaller proportion of participants (≥ 5% absolute difference) in the ponatinib arm compared to the imatinib arm were neutrophil count decreased, anaemia, nausea, vomiting, diarrhoea, oedema peripheral, hypokalaemia, hypoalbuminemia, and periorbital oedema.

Overall, 65.6% vs 59.3% reported a Grade ≥ 3 treatment-related TEAE from the ponatinib arm and the imatinib arm, respectively.

Table 8. PhALLCON: Treatment-Related TEAEs Occurring in ≥ 5% of Participants in Either Study Arm by SOC and PT (Safety Population)

MedDRA SOC **MedDRA PT**	**Ponatinib Arm** **N = 163** **n (%)**	**Imatinib Arm** **N = 81** **n (%)**
Participants with at least 1 treatmentrelated TEAE	141 (86.5)	67 (82.7)
Investigations	103 (63.2)	46 (56.8)
Alanine aminotransferase increased	50 (30.7)	21 (25.9)
Lipase increased	34 (20.9)	20 (24.7)
Aspartate aminotransferase increased	28 (17.2)	9 (11.1)
Neutrophil count decreased	18 (11.0)	17 (21.0)
White blood cell count decreased	15 (9.2)	11 (13.6)
Platelet count decreased	15 (9.2)	10 (12.3)
Amylase increased	11 (6.7)	8 (9.9)
Gammaglutamyltransferase increased	12 (7.4)	4 (4.9)
Blood lactate dehydrogenase increased	9 (5.5)	5 (6.2)
Blood and lymphatic system disorders	57 (35.0)	38 (46.9)
Thrombocytopenia	30 (18.4)	18 (22.2)
Anaemia	24 (14.7)	22 (27.2)
Neutropenia	31 (19.0)	15 (18.5)
Leukopenia	15 (9.2)	8 (9.9)
Febrile neutropenia	11 (6.7)	6 (7.4)
Gastrointestinal disorders	48 (29.4)	41 (50.6)
Nausea	20 (12.3)	24 (29.6)
Vomiting	10 (6.1)	11 (13.6)
Diarrhoea	6 (3.7)	10 (12.3)
Constipation	9 (5.5)	6 (7.4)
General disorders and administration site conditions	33 (20.2)	30 (37.0)
Fatigue	14 (8.6)	8 (9.9)
Oedema peripheral	3 (1.8)	14 (17.3)
Pyrexia	9 (5.5)	4 (4.9)
Metabolism and nutrition disorders	36 (22.1)	27 (33.3)
Hypokalaemia	9 (5.5)	14 (17.3)
Hypophosphataemia	6 (3.7)	7 (8.6)
Hyperuricaemia	11 (6.7)	1 (1.2)
Decreased appetite	4 (2.5)	5 (6.2)
Hypoalbuminaemia	3 (1.8)	6 (7.4)
Hyponatraemia	3 (1.8)	5 (6.2)
Nervous system disorders	32 (19.6)	21 (25.9)
Headache	12 (7.4)	4 (4.9)
Neuropathy peripheral	7 (4.3)	6 (7.4)
Skin and subcutaneous tissue disorders	24 (14.7)	13 (16.0)
Rash	13 (8.0)	4 (4.9)
Vascular disorders	19 (11.7)	1 (1.2)
Hypertension	12 (7.4)	0

MedDRA SOC MedDRA PT	Ponatinib Arm N = 163 n (%)	Imatinib Arm N = 81 n (%)
Eye disorders	8 (4.9)	7 (8.6)
Periorbital oedema	0	5 (6.2)

Note 1: A TEAE is defined as any AE that occurs after administration of the first dose of any study treatment and through 30 days after the last dose of any study treatment.
Note 2: Participants with 1 or more AEs within a level of MedDRA term is counted only once in that level.
Note 3: MedDRA Dictionary v25.0 was used for coding AEs.
Note 4: Data cutoff date of 12 AUG 2022.

TEAEs of Grade 3-4 severity

Grade 3-5 TEAES are summarised in Table 25.

Grade 3 or 4 TEAEs by PT that occurred in a larger proportion of participants (≥ 5% absolute difference) in the ponatinib arm compared to the imatinib arm were thrombocytopenia (45.4% vs 35.8%), ALT increased (19.0% vs 8.6%), AST increased (9.2% vs 3.7%), and hypertension (12.3% vs 6.2%).

Grade 3 or 4 TEAEs by PT that occurred in a smaller proportion of participants (≥ 5% absolute difference) in the ponatinib arm compared to the imatinib arm were anemia (33.1% vs 43.2%), platelet count decreased (21.5% vs 29.6%), neutrophil count decreased (20.9% vs 27.2%), white blood cell count decreased (14.1% vs 19.8%), lipase increased (12.9% vs 18.5%), and hypokalemia (6.1% vs 18.5%).

Grade 3 or 4 serious TEAEs occurred in 52.1% of participants in the ponatinib arm and 45.7% of participants in the imatinib arm.

Table 9 PhALLCON: Grade 3 or Grade 4 TEAEs Occurring in ≥5% of Patients in Either Study Arm by SOC and PT

MedDRA SOC MedDRA PT	Ponatinib Arm (Cohort A) N=163 n (%)	Imatinib Arm (Cohort B) N=81 n (%)
Patients with at least 1 Grade 3 or Grade 4 TEAE	147 (90.2)	75 (92.6)
Blood and lymphatic system disorders	116 (71.2)	58 (71.6)
Thrombocytopenia	74 (45.4)	29 (35.8)
Neutropenia	66 (40.5)	29 (35.8)
Anaemia	54 (33.1)	35 (43.2)
Febrile neutropenia	38 (23.3)	15 (18.5)
Leukopenia	19 (11.7)	8 (9.9)
Investigations	94 (57.7)	49 (60.5)
Platelet count decreased	35 (21.5)	24 (29.6)
Neutrophil count decreased	34 (20.9)	22 (27.2)
White blood cell count decreased	23 (14.1)	16 (19.8)
Alanine aminotransferase increased	31 (19.0)	7 (8.6)
Lipase increased	21 (12.9)	15 (18.5)
Aspartate aminotransferase increased	15 (9.2)	3 (3.7)
Lymphocyte count decreased	2 (1.2)	5 (6.2)
Infections and infestations	50 (30.7)	20 (24.7)
Sepsis	9 (5.5)	2 (2.5)
Metabolism and nutrition disorders	30 (18.4)	25 (30.9)
Hypokalaemia	10 (6.1)	15 (18.5)
Hyperglycaemia	6 (3.7)	6 (7.4)
Gastrointestinal disorders	25 (15.3)	14 (17.3)
Stomatitis	7 (4.3)	7 (8.6)
Nausea	5 (3.1)	6 (7.4)
Vascular disorders	27 (16.6)	6 (7.4)
Hypertension	20 (12.3)	5 (6.2)

Data Cutoff: 12 Aug 2022

Serious adverse event/deaths/other significant events

Deaths due to AE

The rate of on-study deaths due to an AE was similar between the two treatment arms (4.9% in each arm).

Ponatinib: At the data cutoff, a total 8 participants (4.9%) had died due to an adverse event. The reported events were: Septic shock (4 participants [2.5%]) and abdominal sepsis, sepsis, pneumonitis, and respiratory failure (1 participant [0.6%] each). None was considered treatment related.

Imatinib: At the data cutoff, a total of 4 participants (4.9%) had died due to an adverse event. The reported events were: Septic shock, pseudomembranous colitis, pulmonary sepsis, and depressed level of consciousness (1 participant [1.2%] each). One fatal TEAE (depressed level of consciousness) was considered treatment-related.

Other serious adverse events

Serious TEAEs occurred in 59.5% and 55.6% in the ponatinib and imatinib treatment arm, respectively (Table 26).

Table 10. PhALLCON: Treatment Emergent SAEs in ≥ 2 Participants Overall by SOC and PT (Safety Population)

MedDRA SOC MedDRA PT	Ponatinib Arm N = 163 n (%)	Imatinib Arm N = 81 n (%)
Participants with at least 1 serious TEAE	97 (59.5)	45 (55.6)
Infections and infestations	45 (27.6)	18 (22.2)
Septic shock	6 (3.7)	3 (3.7)
COVID-19	7 (4.3)	1 (1.2)
Sepsis	6 (3.7)	2 (2.5)
Pneumonia	4 (2.5)	3 (3.7)
COVID-19 pneumonia	3 (1.8)	2 (2.5)
Cellulitis	2 (1.2)	1 (1.2)
Device related infection	3 (1.8)	0
Urinary tract infection	3 (1.8)	0
Bacteraemia	2 (1.2)	0
Klebsiella sepsis	2 (1.2)	0
Vascular device infection	2 (1.2)	0
Blood and lymphatic system disorders	37 (22.7)	14 (17.3)
Febrile neutropenia	27 (16.6)	12 (14.8)
Thrombocytopenia	6 (3.7)	2 (2.5)
Neutropenia	4 (2.5)	1 (1.2)
Anaemia	4 (2.5)	0
Myelosuppression	1 (0.6)	1 (1.2)
Gastrointestinal disorders	10 (6.1)	7 (8.6)
Pancreatitis	4 (2.5)	0
Stomatitis	1 (0.6)	2 (2.5)
Nervous system disorders	10 (6.1)	5 (6.2)
Haemorrhage intracranial	2 (1.2)	1 (1.2)
Headache	3 (1.8)	0
General disorders and administration site conditions	7 (4.3)	6 (7.4)
Pyrexia	6 (3.7)	3 (3.7)
Investigations	8 (4.9)	3 (3.7)
Platelet count decreased	2 (1.2)	2 (2.5)
Neutrophil count decreased	1 (0.6)	2 (2.5)
Respiratory, thoracic and mediastinal disorders	8 (4.9)	3 (3.7)
Dyspnoea	2 (1.2)	2 (2.5)
Pneumonitis	2 (1.2)	0
Pulmonary embolism	2 (1.2)	0
Injury, poisoning, and procedural complications	5 (3.1)	3 (3.7)

MedDRA SOC MedDRA PT	Ponatinib Arm N = 163 n (%)	Imatinib Arm N = 81 n (%)
Spinal compression fracture	2 (1.2)	0
Subdural haematoma	0	2 (2.5)
Cardiac disorders	5 (3.1)	1 (1.2)
Pericardial effusion	2 (1.2)	0
Metabolism and nutrition disorders	3 (1.8)	3 (3.7)
Hyperglycaemia	1 (0.6)	1 (1.2)
Hypokalaemia	1 (0.6)	1 (1.2)
Musculoskeletal and connective tissue disorders	4 (2.5)	2 (2.5)
Muscular weakness	1 (0.6)	2 (2.5)
Back pain	2 (1.2)	0
Renal and urinary disorders	4 (2.5)	2 (2.5)
Acute kidney injury	3 (1.8)	0
Vascular disorders	3 (1.8)	2 (2.5)
Deep vein thrombosis	1 (0.6)	1 (1.2)

Note 1: A TE-SAE is defined as any SAE that occurs after administration of the first dose of any study treatment and through 30 days after the last dose of any study treatment.
Note 2: Participants with 1 or more AEs within a level of MedDRA term are counted only once in that level.
Note 3: MedDRA Dictionary v25.0 was used for coding AEs.
Note 4: Data cutoff date of 12 AUG 2022.

Adverse events of special interest (AESIs)

Treatment-emergent AOEs

According to the study report, there were 4 TE-AOEs (2.5%) in the ponatinib arm, and one AOE (1.2%) in the imatinib arm (Table 27)

The exposure adjusted-rates (events per 100 person-years) were:

1. Ponatinib: 2.70 (95% CI: 0.04, 5.37)
2. Imatinib: 2.10 (95% CI: 0.00, 6.24)

No fatal AOEs were observed in any treatment arm.

In addition, there was one AOE of stroke in the ponatinib arm that occurred 86 days after the last dose of ponatinib and therefore was not treatment-emergent. The case was therefore not further discussed by the MAH.

Table 27. PhALLCON: TE-AOEs by Adjudicated Result by SOC and PT Sorted by Descending Frequency

MedDRA SOC MedDRA PT	Ponatinib Arm (Cohort A) N=163 n (%)	Imatinib Arm (Cohort B) N=81 n (%)
Patients with at least 1 TE-AOE	4 (2.5)	1 (1.2)
Cardiac disorders	2 (1.2)	0
Acute myocardial infarction	1 (0.6)	0
Angina pectoris	1 (0.6)	0
Nervous System Disorders	1 (0.6)	1 (1.2)
Cerebral infarction	0	1 (1.2)
Lacunar infarction	1 (0.6)	0
Vascular Disorders	1 (0.6)	0
Peripheral arterial occlusive disease	1 (0.6)	0

Data Cutoff: 12 Aug 2022

Serious events

Two participants in the ponatinib arm and 0 participants in the imatinib arm had serious TE-AOEs. These events (acute MI and angina pectoris) were assessed as Grade 3, considered related to study treatment, led to treatment discontinuation, and resolved by the time of data cutoff.

Time to onset

Ponatinib: Median TTO for AOEs was 26.5 days (range: 8-802 days)

Imatinib: TTO of the single AOE was 61.0 days

Recovery

In the ponatinib arm, most AOEs (3 of 4 events [75.0%]) resolved or resolved with sequelae by the time of data cutoff. The one event reported in the imatinib arm also resolved.

Treatment modifications and discontinuations

The two serious TE-AOEs in the ponatinib arm (acute MI and angina pectoris) led to treatment discontinuation.

One additional participant in the ponatinib arm had a nonserious TE-AOE leading to a dose reduction.

Baseline risk factors

Baseline risk factors for participants who experienced TE-AOEs are shown in Table 28. All participants who experienced TE-AOEs (5/5) had a history of hypertension.

Table 28. Baseline risk factors and characteristics of subjects experiencing a TE-AOE in PhALLCON

	Ponatinib Arm (Cohort A) N=4	Imatinib Arm (Cohort B) N=1	Total N=5
History of Ischaemic Heart Disease			
Yes	1 (25.0)	0	1 (20.0)
No	3 (75.0)	1 (100.0)	4 (80.0)
History of Diabetes Mellitus			
Yes	1 (25.0)	1 (100.0)	2 (40.0)
No	3 (75.0)	0	3 (60.0)
History of Smoking			
Yes	1 (25.0)	0	1 (20.0)
No	3 (75.0)	1 (100.0)	4 (80.0)
History of Obesity			
Yes	0	1 (100.0)	1 (20.0)
No	4 (100.0)	0	4 (80.0)
History of Hypertension			
Yes	4 (100.0)	1 (100.0)	5 (100.0)
No	0	0	0
History of Dyslipidaemia			
Yes	1 (25.0)	1 (100.0)	2 (40.0)
No	3 (75.0)	0	3 (60.0)

Treatment-emergent VTEs

A summary of TE-VTEs, including time-to-onset is provided in Table 29.

The overall rate of VTEs was 11.7% in the ponatinib arm and 12.3% in the imatinib arm. The exposure adjusted rates were 14.0 in the ponatinib arm and 22.4 in the imatinib arm.

Of the 29 participants who had TE-VTEs, 48.2% (8 participants in the ponatinib arm and 6 participants in the imatinib arm) had events assessed as related to the use of peripherally inserted central catheter lines or central venous catheter for delivery of chemotherapy.

The most common TE-VTEs that occurred in ≥ 2 participants in either the ponatinib or imatinib arms were deep vein thrombosis (4.3% vs 7.4%), embolism (1.8% vs 1.2%), superficial vein thrombosis (1.8% vs 0%), pulmonary embolism (1.2% vs 1.2%), and device-related thrombosis (1.2% vs 0%).

Table 29. Summary of TE-VTEs by Adjudicated Result by Treatment

	Ponatinib Arm (Cohort A) N=163 n (%)	Imatinib Arm (Cohort B) N=81 n (%)
TE-VTEs	19 (11.7)	10 (12.3)
Grade 3-4	6 (3.7)	1 (1.2)
Grade 5	0	0
Treatment-related	8 (4.9)	1 (1.2)
Grade 3-4 treatment-related	2 (1.2)	0
Grade 5 treatment-related	0	0
Leading to treatment discontinuation	0	0
Leading to dose reduction	0	0
Leading to dose interruption	9 (5.5)	0
PICC-line or CVC-related VTEs	8 (4.9)	6 (7.4)
Serious TE-VTEs	3 (1.8)	2 (2.5)
Grade 3-4	2 (1.2)	0
Grade 5	0	0
Treatment-related	2 (1.2)	0
Grade 3-4 treatment-related	1 (0.6)	0
Grade 5 treatment-related	0	0
Leading to treatment discontinuation	0	0
Leading to dose reduction	0	0
Leading to dose interruption	2 (1.2)	0
PICC-line or CVC-related VTEs	1 (0.6)	2 (2.5)
Days on study when first TE-VTE observed		
n	19	10
Mean (SD)	113.5 (150.06)	86.7 (41.31)
Median	71.0	82.0
Min, max	5, 666	39, 170
Dose intensity during last 30 days prior to first occurred TE-VTE (mg/day)		
n	19	10
Mean (SD)	23.79 (7.997)	558.34 (71.963)
Median	30.00	600.00
Min, max	10.0, 30.0	386.7, 600.0

Data Cutoff: 12 Aug 2022

Table 11. PhALLCON: Exposure-adjusted TE-VTEs

Study Arm	Number of Treated Patients	Patients with VTEs	Total Person-Years	Exposure Adjusted VTE Rate (95% CI)
Ponatinib arm (Cohort A)	163	19	135.39	14.03 (7.35, 20.72)
Imatinib arm (Cohort B)	81	10	44.64	22.40 (7.55, 37.25)

Table 12. PhALLCON: TE-VTEs by SOC and PT

MedDRA SOC MedDRA PT	Ponatinib Arm (Cohort A) N=163 n (%)	Imatinib Arm (Cohort B) N=81 n (%)
Patients with any TE-VTEs	19 (11.7)	10 (12.3)
Vascular disorders	15 (9.2)	9 (11.1)
Deep vein thrombosis	7 (4.3)	6 (7.4)
Embolism	3 (1.8)	1 (1.2)
Superficial vein thrombosis	3 (1.8)	0
Axillary vein thrombosis	0	1 (1.2)
Brachiocephalic vein thrombosis	0	1 (1.2)
Phlebitis	1 (0.6)	0
Thrombosis	1 (0.6)	0
Venous thrombosis	1 (0.6)	0
Respiratory, thoracic, and mediastinal disorders	2 (1.2)	1 (1.2)
Pulmonary embolism	2 (1.2)	1 (1.2)
General disorders and administration site conditions	2 (1.2)	0
Device related thrombosis	2 (1.2)	0
Cardiac disorders	1 (0.6)	0
Cardiac failure congestive	1 (0.6)	0
Eye disorders	1 (0.6)	0
Retinal vein occlusion	1 (0.6)	0

Data Cutoff: 12 Aug 2022

Treatment-related TE-VTEs

TE-VTEs that were considered treatment-related are summarised in Table 32.

Table 13. Treatment-Related TE-VTEs by Adjudicated Result by SOC and PT

MedDRA SOC MedDRA PT	Ponatinib Arm (Cohort A) N=163 n (%)	Imatinib Arm (Cohort B) N=81 n (%)
Patients with any treatment-related TE-VTEs	8 (4.9)	1 (1.2)
Vascular disorders	6 (3.7)	1 (1.2)
Deep vein thrombosis	3 (1.8)	1 (1.2)
Embolism	2 (1.2)	0
Superficial vein thrombosis	1 (0.6)	0
Thrombosis	1 (0.6)	0
Respiratory, thoracic, and mediastinal disorders	2 (1.2)	0
Pulmonary embolism	2 (1.2)	0
Cardiac disorders	1 (0.6)	0
Cardiac failure congestive	1 (0.6)	0
Eye disorders	1 (0.6)	0
Retinal vein occlusion	1 (0.6)	0

Data Cutoff: 12 Aug 2022

Serious TE-VTEs

Ponatinib: Three participants (1.8%) in the ponatinib arm had serious TE-VTEs, of which two were considered treatment-related (both were pulmonary embolism and assessed as Grade 2 or Grade 3). The events were managed with dose interruptions and resolved by the time of data cutoff.

Imatinib: Two participants (2.5%) in the imatinib arm had serious TE-VTEs (deep vein thrombosis and brachiocephalic vein thrombosis, respectively, both were assessed as Grade 2), of which none were considered treatment-related.

Recovery

Ponatinib: 16 of 23 VTEs (69.6%) resolved

Imatinib: 6 of 10 events (60%) resolved

Median time to event resolution was 31.0 days (95% CI: 15.0, NE) in the ponatinib arm compared to 73.0 days (95% CI: 4.0, NE) in the imatinib arm.

Treatment modifications and discontinuations

No participants in either study arm discontinued study treatment due to a TE-VTE.

A total of 11 participants in the ponatinib arm had TE-VTEs leading to dose interruptions.

No TE-VTEs in the imatinib arm led to dose interruption or dose reduction.

Cardiovascular Risk factors and antithrombotic treatment

An excerpt of the data on medical history or the safety population, including some baseline risk factors/medical history that could affect the risk for VOEs are summarised in Table 33 below.

Concomitant prothrombotic treatment is shown in Table 34.

Table 14. PhALLCON: Medical History by System Organ Class and Preferred Term by Treatment Arm (selection)

System Organ Class Preferred Term	Ponatinib Arm (Cohort A) (N=164) n (%)	Imatinib Arm (Cohort B) (N=81) n (%)	Total (N=245) n (%)
Subjects with Any Reported Medical History	151 (92.1)	77 (95.1)	228 (93.1)
Metabolism and nutrition disorders	64 (39.0)	44 (54.3)	108 (44.1)
Hyperglycaemia	18 (11.0)	9 (11.1)	27 (11.0)
Diabetes mellitus	11 (6.7)	8 (9.9)	19 (7.8)
Obesity	12 (7.3)	7 (8.6)	19 (7.8)

Type 2 diabetes mellitus	8 (4.9)	8 (9.9)	16 (6.5)
Hyperlipidaemia	9 (5.5)	5 (6.2)	14 (5.7)
Dyslipidaemia	8 (4.9)	5 (6.2)	13 (5.3)
Hypertriglyceridaemia	8 (4.9)	4 (4.9)	12 (4.9)
Hypercholesterolaemia	4 (2.4)	6 (7.4)	10 (4.1)
Hyperuricaemia	6 (3.7)	2 (2.5)	8 (3.3)
Decreased appetite	4 (2.4)	3 (3.7)	7 (2.9)
Hypoalbuminaemia	2 (1.2)	4 (4.9)	6 (2.4)
Hyperphosphataemia	5 (3.0)	0	5 (2.0)
Hypocalcaemia	4 (2.4)	1 (1.2)	5 (2.0)
Vitamin D deficiency	1 (0.6)	3 (3.7)	4 (1.6)
Folate deficiency	2 (1.2)	1 (1.2)	3 (1.2)
Glucose tolerance impaired	1 (0.6)	2 (2.5)	3 (1.2)
Gout	1 (0.6)	1 (1.2)	2 (0.8)
Hyperkalaemia	2 (1.2)	0	2 (0.8)
Hypomagnesaemia	1 (0.6)	1 (1.2)	2 (0.8)
Hypophosphataemia	1 (0.6)	1 (1.2)	2 (0.8)
Hypoproteinaemia	2 (1.2)	0	2 (0.8)
Tumour lysis syndrome	0	2 (2.5)	2 (0.8)
Vitamin B12 deficiency	1 (0.6)	1 (1.2)	2 (0.8)
Cell death	0	1 (1.2)	1 (0.4)
Central obesity	1 (0.6)	0	1 (0.4)
Dehydration	0	1 (1.2)	1 (0.4)
Electrolyte imbalance	1 (0.6)	0	1 (0.4)
Fluid retention	0	1 (1.2)	1 (0.4)
Hyperlipasaemia	1 (0.6)	0	1 (0.4)
Hypokalaemia	1 (0.6)	0	1 (0.4)
Hyponatraemia	1 (0.6)	0	1 (0.4)
Insulin resistance	1 (0.6)	0	1 (0.4)
Lactose intolerance	1 (0.6)	0	1 (0.4)
Malnutrition	0	1 (1.2)	1 (0.4)
Overweight	1 (0.6)	0	1 (0.4)
Steroid diabetes	1 (0.6)	0	1 (0.4)
Type 1 diabetes mellitus	0	1 (1.2)	1 (0.4)
Vascular disorders	65 (39.6)	31 (38.3)	96 (39.2)
Hypertension	54 (32.9)	27 (33.3)	81 (33.1)
Essential hypertension	3 (1.8)	2 (2.5)	5 (2.0)
Superficial vein thrombosis	3 (1.8)	0	3 (1.2)
Deep vein thrombosis	1 (0.6)	1 (1.2)	2 (0.8)
Varicose vein	1 (0.6)	1 (1.2)	2 (0.8)
Venous thrombosis	1 (0.6)	1 (1.2)	2 (0.8)
Aortic stenosis	0	1 (1.2)	1 (0.4)
Arteriosclerosis	0	1 (1.2)	1 (0.4)
Granulomatosis with polyangiitis	1 (0.6)	0	1 (0.4)
Haematoma	1 (0.6)	0	1 (0.4)
Haemorrhage	0	1 (1.2)	1 (0.4)
Hot flush	0	1 (1.2)	1 (0.4)
May-Thurner syndrome	0	1 (1.2)	1 (0.4)
Orthostatic hypotension	1 (0.6)	0	1 (0.4)
Peripheral venous disease	1 (0.6)	0	1 (0.4)
Phlebitis	1 (0.6)	0	1 (0.4)
Systolic hypertension	1 (0.6)	0	1 (0.4)

Source: Ponatinib-3001 Clinical Study report, table 15.1.4.3

Table 15. PhALLCON: Concomitant antithrombotic treatment

ANTITHROMBOTIC AGENTS	72 (43.9)	29 (35.8)	101 (41.2)
ENOXAPARIN	22 (13.4)	11 (13.6)	33 (13.5)
ENOXAPARIN SODIUM	25 (15.2)	8 (9.9)	33 (13.5)
ACETYLSALICYLIC ACID	21 (12.8)	1 (1.2)	22 (9.0)
ALTEPLASE	8 (4.9)	3 (3.7)	11 (4.5)
HEPARIN	7 (4.3)	3 (3.7)	10 (4.1)
APIXABAN	7 (4.3)	2 (2.5)	9 (3.7)
RIVAROXABAN	2 (1.2)	3 (3.7)	5 (2.0)
DALTEPARIN SODIUM	3 (1.8)	1 (1.2)	4 (1.6)
TINZAPARIN SODIUM	2 (1.2)	2 (2.5)	4 (1.6)
FONDAPARINUX	3 (1.8)	0	3 (1.2)
FONDAPARINUX SODIUM	3 (1.8)	0	3 (1.2)
NADROPARIN CALCIUM	2 (1.2)	1 (1.2)	3 (1.2)
TINZAPARIN	3 (1.8)	0	3 (1.2)
ACETYLSALICYLATE LYSINE	2 (1.2)	0	2 (0.8)
ALPROSTADIL	2 (1.2)	0	2 (0.8)
HEPARIN SODIUM	2 (1.2)	0	2 (0.8)
BEMIPARIN SODIUM	1 (0.6)	0	1 (0.4)
CLOPIDOGREL	0	1 (1.2)	1 (0.4)
DABIGATRAN ETEXILATE MESILATE	1 (0.6)	0	1 (0.4)
DALTEPARIN	0	1 (1.2)	1 (0.4)
LOW MOLECULAR WEIGHT HEPARIN	0	1 (1.2)	1 (0.4)
STREPTOKINASE	0	1 (1.2)	1 (0.4)

Source: Ponatinib-3001 Clinical Study report, table 15.1.5.2

Hepatotoxicity

Hepatotoxicity occurred in a higher proportion of patients in the ponatinib arm: 105 patients (64.4%) in the ponatinib arm compared to 46 patients (56.8%) in the imatinib arm.

There were no fatal (Grade 5) events. In the ponatinib arm, treatment-related serious events included ALT increased and blood bilirubin unconjugated increased (reported in 1 patient each). No patients in the imatinib arm experienced serious events.

Severe (Grade 3 or 4) hepatotoxicity TEAEs occurred in a higher proportion of patients in the ponatinib arm: 46 patients (28.2%) in the ponatinib arm compared to 11 patients (13.6%) in the imatinib arm.

One case of DILI (grade <3) was reported in the ponatinib arm.

No case of Hy's law was reported.

Other AESI:s

Other TEAEs of interest included cardiac failure, arrhythmias including QT prolongation, pancreatitis, and amylase or lipase elevations, myelosuppression, haemorrhage, fluid retention, and hypertension.

Cardiac failure occurred in 4 patients (2.5%) in the ponatinib arm compared to 4 patients (4.9%) in the imatinib arm. There were no fatal (Grade 5) events. One patient (0.6%) in the ponatinib arm experienced the serious event of cardiac failure, which was assessed as treatment related and led to treatment discontinuation.

Cardiac arrhythmia occurred in 29 patients (17.8%) in the ponatinib arm compared to 13 patients (16.0%) in the imatinib arm. There were no fatal (Grade 5) events. In the imatinib arm, serious events included atrial fibrillation and syncope (reported in 1 patient each) Severe (Grade 3 or 4) cardiac arrhythmia TEAEs occurred in 2 patients (1.2%) in the ponatinib arm and 4 patients (4.9%) in the imatinib arm. The most common PTs in the ponatinib arm were tachycardia (6.7%) and palpitations (3.7%), whereas the most common PTs in the imatinib arm were tachycardia (6.2%), as well as sinus tachycardia and syncope (4.9% each).

Clinical pancreatitis occurred in 6 patients (3.7%) in the ponatinib arm compared to 0 patients in the imatinib arm; 5 patients (3.1%) in the ponatinib arm had events that were assessed as treatment related. There were no fatal (Grade 5) events. Four patients (2.5%) in the ponatinib arm experienced serious events of pancreatitis that were all assessed as treatment related. There were no fatal (Grade 5) events. Four patients (2.5%) in the ponatinib arm experienced serious events of pancreatitis that were all assessed as treatment related.

Chemical pancreatitis occurred in 48 patients (29.4%) in the ponatinib arm compared to 30 patients (37.0%) in the imatinib arm. There were no serious or fatal (Grade 5) events.

Myelosuppression occurred in 135 patients (82.8%) in the ponatinib arm compared to 71 (87.7%) patients in the imatinib arm. There were no fatal (Grade 5) events. Serious events occurring in more than 1 patient included (ponatinib arm vs imatinib arm) febrile neutropenia (27 patients [16.6%] vs 12 patients [14.8%]), thrombocytopenia (6 patients [3.7%] vs 2 patients [2.5%]), neutropenia (4 patients [2.5%] vs 1 patient [1.2%]), anaemia (4 patients [2.5%] vs 0 patients), platelet count decreased (2 patients [1.2%] vs 2 patients [2.5%]), and neutrophil count decreased (1 patient [0.6%] vs 2 patients [2.5%]). Severe (Grade 3 or 4) myelosuppression TEAEs occurred in a similar proportion of patients across treatment arms: 66 patients (40.5%) in the ponatinib arm compared to 44 patients (54.3%) in the imatinib arm. Events that led to treatment discontinuation occurred in 2 patients (1.2%) in the ponatinib arm compared to 1 patient (1.2%) in the imatinib arm. Events leading to dose

interruption occurred in 48 patients (29.4%) in the ponatinib arm compared to 16 patients (19.8%) in the imatinib arm. Events leading to dose reduction occurred in 7 patients (4.3%) in the ponatinib arm compared to 14 patients (17.3%) in the imatinib arm.

Haemorrhage occurred in 45 patients (27.6%) experienced in the ponatinib arm compared to 24 patients (29.6%) in the imatinib arm. There were no fatal (Grade 5) events. Serious events included (ponatinib arm vs imatinib arm) subdural haematoma (0 patients vs 2 patients [2.5%]), post procedural haematuria (1 patient [0.6%] vs 0 patients), and vascular pseudoaneurysm ruptured (1 patient [0.6%] vs 0 patients). Severe (Grade 3 or 4) haemorrhage TEAEs occurred in 3 patients (1.8%) in the ponatinib arm and 6 patients (7.4%) in the imatinib arm. No severe (Grade 3 or 4) haemorrhage TEAEs were considered treatment related. No patients experienced events that led to treatment discontinuation or dose reduction. Events leading to dose interruption occurred in 2 patients (1.2%) in the ponatinib arm compared to 5 patients (6.2%) in the imatinib arm. The most common PTs in the ponatinib arm were petechiae and epistaxis (5.5% each), whereas the most common PTs in the imatinib arm were haematuria (4.9%) as well as contusion and vaginal haemorrhage (3.7% each).

Fluid retention occurred in a lower proportion of patients in the ponatinib arm: 34 patients (20.9%) in the ponatinib arm compared to 35 patients (43.2%) in the imatinib arm. There were no fatal (Grade 5) events. Serious events included (ponatinib arm vs imatinib arm) pericardial effusion (2 patients [1.2%] vs 0 patients), generalised oedema (0 patients vs 1 patient [1.2%]), and pleural effusion (0 patients vs 1 patient [1.2%]). A total of 1 patient in the ponatinib arm experienced an event that led to treatment discontinuation. Events leading to dose interruption occurred in 3 patients (1.8%) in the ponatinib arm compared to 3 patients (3.7%) in the imatinib arm. Events leading to dose reduction occurred in 1 patient (0.6%) in the ponatinib arm compared to 1 patient (1.2%) in the imatinib arm.

Hypertension occurred in a higher proportion of patients in the ponatinib arm: 52 patients (31.9%) in the ponatinib arm compared to 11 patients (13.6%) in the imatinib arm. There were no serious or fatal (Grade 5) events. No patients experienced events that led to treatment discontinuation or dose reduction. Events leading to dose interruption occurred in 2 patients (1.2%) in the ponatinib arm compared to 0 patients in the imatinib arm.

Laboratory findings

Clinical chemistry

Overall, there were no notable changes in clinical chemistry mean observed values or mean changes from baseline in either treatment arm. Clinical chemistry parameters in which >1 patient overall had a Grade 3 or 4 laboratory abnormality are shown in Table 35.

Table 16. PhALLCON: Grade 3 or 4 Chemistry Laboratory Abnormalities in >1 Patient

Laboratory Test (Worsening from baseline to Grade 3 or 4)	Ponatinib Arm (Cohort A) N=163 n (%)	Imatinib Arm (Cohort B) N=81 n (%)
Lipase increased	38 (23.3)	29 (35.8)
ALT increased	29 (17.8)	7 (8.6)
AST increased	9 (5.5)	5 (6.2)
Direct bilirubin increased	7 (4.3)	1 (1.2)
Serum amylase increased	3 (1.8)	1 (1.2)
Creatinine increased	2 (1.2)	2 (2.5)

Haematology

Mean increases from baseline for haemoglobin were observed more frequently in the ponatinib arm compared to the imatinib arm. Mean increases from baseline in neutrophils and platelets were observed with similar frequency across study arms. Haematology parameters in which >1 patient overall had a Grade 3 or 4 laboratory abnormality are shown in Table 36.

Table 17. PhALLCON: Grade 3 or 4 Haematologic Laboratory Abnormalities in >1 Patient

Laboratory Test (Worsening from baseline to Grade 3 or 4)	Ponatinib Arm (Cohort A) N=163 n (%)	Imatinib Arm (Cohort B) N=81 n (%)
Platelet count decreased	103 (63.2)	47 (58.0)
White blood cell decreased	87 (53.4)	40 (49.4)
Neutrophil count decreased	80 (49.1)	37 (45.7)
Lymphocyte count decreased	62 (38.0)	38 (46.9)
Anaemia	50 (30.7)	29 (35.8)

Discontinuation due to adverse events

TEAEs leading to study drug discontinuation occurred in 17 patients (10.4%) in the ponatinib arm and 7 patients (8.6%) in the imatinib arm (Table 37).

Two patients (ponatinib arm) discontinued treatment due to an AOE. No patient discontinued treatment due to a VTE.

Table 37. PhALLCON: TEAEs Leading to Study Drug Discontinuation Occurring in >1 Patient Overall

MedDRA SOC MedDRA PT	Ponatinib Arm (Cohort A) N = 163 n (%)	Imatinib Arm (Cohort B) N = 81 n (%)
Patients with at least 1 TEAE leading to study drug discontinuation	17 (10.4)	7 (8.6)
Infections and infestations	4 (2.5)	2 (2.5)
Septic shock	2 (1.2)	1 (1.2)
Sepsis	2 (1.2)	0
Investigations	4 (2.5)	1 (1.2)
Alanine aminotransferase increased	3 (1.8)	0
Aspartate aminotransferase increased	2 (1.2)	0

Data Cutoff: 12 Aug 2022

2.5.1. Discussion on clinical safety

The MAH has applied for an indication for ponatinib in combination with reduced-intensity chemotherapy in adult patients with newly diagnosed Ph+ ALL.

One concern with using ponatinib treatment in an earlier line of treatment, as compared with the 1st and 2nd generation TKIs previously approved for this indication (imatinib and dasatinib), has been the pro-thrombotic properties of ponatinib. For the previous indications, a recommendation to consider dose reductions in patients who have responded to treatment was introduced in the Iclusig SmPC at an early stage, following an Art 20 referral. Subsequently, data from a dose-optimising trial (OPTIC) has substantiated that the VOE risk is exposure dependent and, thus, decreases following dose reductions.

For the currently applied indication the MAH suggests a 'mandatory' dose reduction following achievement of MRD-negative CR, in line with the pivotal study (PhALLCON) protocol. Furthermore, the starting dose of ponatinib is lower (30 mg) than for the monotherapy indications (45 mg).

Safety database

The safety assessment for the current application relies primarily on the submitted pivotal study, Study Ponatinib-3001 (PhALLCON). This is an ongoing, multicenter, open-label, Phase 3 study comparing ponatinib + reduced intensity chemotherapy with imatinib + reduced intensity chemotherapy in patients with newly diagnosed Ph+ ALL. The starting dose for ponatinib in the study is 30 mg QD, with a dose reduction to 15 mg QD in patients who achieves MRD-negative CR, (ie. the same dose recommendation as that proposed for the new indication in the SmPC, section 4.2). The number of subjects is 164 in the ponatinib arm and 81 in the imatinib arm.

The MAH also submitted two supportive studies. Their relevance for the currently applied indication and dose regimen is, however, limited:

- Study AP24534-11-001 was an investigator-sponsored, single-center, single arm study of ponatinib + intensive chemotherapy (hyper-CVAD) in 87 patients with newly diagnosed Ph+ ALL. The starting dose of ponatinib was higher in this study (45 mg) than what is currently proposed for the combination with chemotherapy (30 mg). The recommendation of a prospective dose reduction in subjects responding to treatment was not introduced in the study protocol until 43% of the patients had been treated. There was a multitude of protocol amendments, including the changes in dose recommendations, and it is unclear how the safety population might have changed over time. It was difficult to deduce how many cycles of chemotherapy patients had actually received. The small study population and the lack of a control arm in this study further limits the possibility to draw informed conclusions on the acceptability of the safety profile of ponatinib in combination with more intense chemotherapy.
- Study INCB 84344-201 was a small (n=44) single-arm study on ponatinib as monotherapy to patients with Ph+ ALL who were not fit for intensive chemotherapy and HSCT. The study did not include the recommendation of a prospective dose reduction in subjects responding to treatment. From a safety perspective, this study is not adding much information compared with previous data on ponatinib as monotherapy. Further, the study was performed in a frail population, which e.g. due to age may be more prone to cardiovascular events than the population encompassed by the currently applied indication.

Therefore, the available safety data for the proposed indication and dosage is limited to the pivotal study, PhALLCON. As the available safety data do not allow sufficiently informed conclusions on the tolerability of ponatinib in combination with a more intense chemotherapy backbone than that administered in PhALLCON, the indication is restricted to combination of ponatinib with reduced-intensity chemotherapy.

Analysis of the currently available data

The data cutoff for the PhALLCON data presented with the current submission is 12 August 2022. At the data cutoff, the median duration of exposure was longer in the ponatinib arm (7.3 months) than in

the imatinib arm (5.1 months), and 41.5% of patients were still on treatment in the ponatinib arm, while only 12.3% had treatment ongoing in the imatinib arm. There was no relevant difference in discontinuation to AEs, but the difference was mainly in discontinuations due to lack of efficacy. Characterisation of the risk for VOEs, and in particular AOEs, during longer-term treatment in this patient population is desirable. The MAH will provide an updated analysis of VOEs (AOEs and VTEs) once the study is unblinded.

Based on the currently available data, the difference in the exposure-adjusted rate of treatment-emergent AOEs was 2.7 per 100 patient years in the ponatinib arm 2.1 per 100 patient years in the imatinib arm. There were no fatal AOEs, but two serious events (acute MI and angina pectoris) in the ponatinib arm led to treatment discontinuation. In the PACE trial, which was the registrational study for ponatinib monotherapy in resistant CML or Ph+ ALL, and which was performed before introduction of prospective dose reductions and with a starting dose of 45 mg, the exposure-adjusted rate of AOEs was 13.8% per 100 patient years. The data from PhALLCON suggest that with the lower starting dose and the prospective dose reductions, the prothrombotic risk for ponatinib may be sufficiently manageable. The new posology consisting of a 30 mg starting dose once daily followed by a dose reduction to 15mg once daily upon achievement of MRD-negative complete response, with a potential for re-escalation in case of loss of efficacy has been reflected in Section 4.2.

The SmPC already includes a recommendation that cardiovascular status should be monitored and medical and supportive therapy for conditions that contribute to cardiovascular risk should be optimised during treatment with ponatinib.

The rate of VTEs was higher in the imatinib arm (12.3%) than in the ponatinib arm (11.7%) without taking the difference in exposure into account. The exposure adjusted VTE rate was 22.4 and 14.0 per 100 patient years in the imatinib arm and the ponatinib arm, respectively. The nominal differences in cardiovascular risk factors and antithrombotic treatment between the two treatment groups are not considered to impact the interpretability of data.

In terms of the general safety profiles, the overall proportion of treatment-emergent adverse events (TEAEs; 99.4% and 99.8% in the ponatinib and imatinib arms respectively) and TEAEs considered treatment-related (86.5% and 82.7%, respectively) was similar between treatment groups.

The most commonly reported events were qualitatively similar between the treatment arms, although there were differences in the rates of some PTs.

Myelosuppression, including Grade 3-4 events, were reported to a similar or lower rate in the ponatinib arm compared with the imatinib arm (82.8% vs. 87.7%; Grade 3-4: 40.5% vs. 54.3%). On the other hand, a higher rate of TEAEs within the SOC Infections and infestations was reported for ponatinib than for imatinib (70.6% vs 55.6%) with Covid-19 the most commonly reported PT (16.0% vs. 9.9%). The most commonly reported Grade 3-4 infection was sepsis (5.5% and 2.5% in the ponatinib and imatinib arms, respectively). The difference in rate of treatment-emergent infections can possibly be explained by the difference in treatment duration between the two groups.

Overall, Grade 3 - 4 TEAEs of all causality occurred in a comparable proportion of participants in the two treatment arms (90.2% and 92.6%, respectively), and the most commonly reported Grade 3-4 TEAEs were largely similar. These included e.g. events associated with myelosuppression, infections, gastrointestinal disorders and investigations. Also serious TEAEs occurred in a similar proportion of participants in the ponatinib arm (59.5%) and the imatinib arm (55.6%).

The rate of deaths due to an AE was similar (4.9%) in the two treatment arms. None of the 8 deaths due to AE in the ponatinib arm and one of the 4 deaths in the imatinib arm (depressed level of

consciousness) was considered treatment related. There were no deaths due to a VOE in either treatment arm.

Hepatotoxicity was reported at a slightly higher rate in the ponatinib arm (64%) than in the imatinib arm (56.8%). Hepatotoxicity is a known effect of both TKIs and is sufficiently well described in the SmPC, with relevant risk minimisation measures. A warning has been added in section 4.4 of the Iclusig SmPC that the risk for hepatotoxicity is increased at combination with hepatotoxic chemotherapeutic agents, which is in line with information in the imatinib SmPC.

The rate of discontinuations due to AEs were similar between the treatment groups (10.4% and 8.6% in the ponatinib and imatinib arms, respectively). TEAEs (PTs) leading to treatment discontinuations reported in more than one subject in the ponatinib arm were sepsis/septic shock and ALT or AST increased. There were two AOEs that led to discontinuation, as described above.

The rate of dose interruptions due to TEAEs was higher in the ponatinib arm (68.1%) than in the imatinib arm (39.5%). The MAH suggests that this is at least in part due to more conservative dose modification guidelines in the Study Protocol and in the prescribing information for ponatinib than in the prescribing information for imatinib.

The MAH has proposed a new table in section 4.8 of the SmPC to describe the safety data from PhALLCON. It is considered adequate to have separate ADR tables for the monotherapy and the combination treatments.

2.5.2. Conclusions on clinical safety

No new safety concerns have been identified for ponatinib 30 mg in combination with reduced-intensity chemotherapy in patients with newly diagnosed Ph+ ALL. With the prospective dose reduction in patients responding to treatment, the safety profile appears to be manageable and not substantially worse than that of the comparator, imatinib. The rate of AOEs, when adjusted for differences in treatment duration, was comparable to the rate observed in the imatinib arm. The database is, however, relatively small and the number of AOEs was low at the data cutoff, when ponatinib treatment was still ongoing in a large proportion of patients. The MAH has committed to provide an updated analysis of AOEs and VTEs with the final study report of the PhALLCON study (see Annex II).

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version 24.1 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 24.1 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

No changes are proposed to the Summary of safety concerns.

Summary of safety concerns	

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

Important potential risks	Teratogenicity
Missing information	None

Pharmacovigilance plan

No changes are proposed to the Pharmacovigilance plan.

The MAH has committed to provide updated safety data on VOEs from the PhALLCON study. The study is therefore briefly described in Part III.2 of the RMP, although it is not considered an additional Pharmacovigilance activity.

Post-authorisation efficacy studies

Submission of the final efficacy data from the PhALLCON study is an Annex II condition, which is also described in Section IV of the RMP.

Risk minimisation measures

No changes are proposed to the risk minimisation measures.

2.7. Update of the Product information

As a result of this variation, section 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are being updated to modify the currently approved therapeutic indication to include treatment of adult patients with newly-diagnosed Ph+ ALL.

The Package Leaflet (PL) is updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

There have not been revisions that significantly affect the overall readability and design of the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Use of ponatinib in combination with reduced-intensity chemotherapy in adult patients with newly diagnosed Ph+ ALL.

3.1.2. Available therapies and unmet medical need

The ESMO interim guideline of 2023 specified that reduced-intensity chemotherapy and a first- or second-generation TKI followed by allo-HSCT is considered the standard therapy for patients with newly diagnosed Ph+ ALL.

In the EU, imatinib is currently the only approved TKI therapy for adult patients with newly diagnosed Ph+ ALL, as integrated with chemotherapy. In second line and later, monotherapy with dasatinib as well as ponatinib are approved.

There is an unmet medical need for new treatments that can suppress the development of mutations, thus preventing the sequencing of multiple treatments (including HSCT) and resulting in long-term clinical benefit.

3.1.3. Main clinical study

The pivotal study Ponatinib-3001 (PhALLCON) is an ongoing, phase 3, randomized, open-label, multicenter study comparing ponatinib (n=164) versus imatinib (n=81), administered in combination with reduced-intensity chemotherapy, in patients with newly diagnosed Ph+ ALL.

The primary endpoint is MRD-negative CR at the end of induction therapy. The key secondary endpoint is EFS, defined as the date of randomization until death due to any cause; failure to achieve CR by the end of induction or relapse from CR.

Participants were randomized in a 2:1 ratio to receive ponatinib (ponatinib arm) or imatinib (imatinib arm) QD. Both TKIs were administered in combination with reduced intensity chemotherapy for 3 cycles of induction therapy, 6 cycles of consolidation therapy, and 11 cycles of maintenance therapy, followed by treatment with single-agent ponatinib or imatinib administered continuously after Cycle 20.

Participants randomized to the ponatinib arm received a starting dose of 30 mg ponatinib QD, with a dose reduction to 15 mg QD if they achieved MRD negative CR by the EOI (end of Cycle 3) or later.

3.2. Favourable effects

Among the 232 participants in the ITT population with a baseline p190 or p210 variant, the MRD-negative CR rate at EOI was 34.4% for ponatinib, compared to 16.7% for imatinib with a p-value of 0.0021. Presented subgroup results of the primary endpoint showed an overall consistent treatment effect.

Regarding EFS the prespecified number of events for analysis had not been reached at the time of the data cutoff. Median EFS was not reached for the ponatinib arm whereas it was 29.04 months (95% CI: 22.29, NE) for the imatinib arm with a HR of 0.652 (95% CI: 0.385, 1.104). Although the difference in EFS was not statistically significant, the trend favoured ponatinib.

OS results were also immature at the time of analysis, with 21 events (12.8%) reported in the ponatinib arm and 13 events (16.0%) in the imatinib arm. Median OS was not reached in either treatment arm. The OS trend favoured ponatinib, with a HR 0.761 (95% CI: 0.381, 1.520), although the difference was not statistically significant.

3.3. Uncertainties and limitations about favourable effects

It is unclear if and to what extent the increased rate of MRD negative CR translates into an increase in EFS and OS, compared to imatinib.

An exploratory analysis demonstrated that the proportion of participants with HSCT events was higher in the imatinib arm (48.1%) compared to the ponatinib arm (34.1%). The fact that fewer patients in the ponatinib arm underwent HSCT does not, in itself, provide sufficient evidence to support the omission of HSCT in patients treated with ponatinib, since HSCT was not randomized and the decision to proceed with HSCT was made after the assessment of the primary end point in this open-label trial.

3.4. Unfavourable effects

The adverse event profile of ponatinib 30 mg in combination with reduced-intensity chemotherapy was qualitatively similar to that of imatinib in combination with reduced-intensity chemotherapy and to that of ponatinib monotherapy (45 mg starting dose), although with some quantitative differences. The overall rates of TEAEs (99.4% and 98.8% in the ponatinib arm and imatinib arm, respectively), and the rates of Grade 3-4 TEAEs (90.2% and 92.6%, respectively) were similar.

Myelosuppression, including Grade 3-4 events, were reported to a similar or lower rate in the ponatinib arm compared with the imatinib arm (82.8% vs. 87.7%; Grade 3-4: 40.5% vs. 54.3%). On the other hand, a higher rate of TEAEs within the SOC Infections and infestations was reported for ponatinib than for imatinib (70.6% vs 55.6%) with Covid-19 the most commonly reported PT (16.0% vs. 9.9%). The most commonly reported Grade 3-4 infection was sepsis (5.5% and 2.5% in the ponatinib and imatinib arms, respectively).

Hepatotoxicity was reported at a slightly higher rate in the ponatinib arm (64%) than in the imatinib arm (56.8%). This is a well-known AE with BCL-ABL targeting TKI’s.

The rate of arterial occlusive events (AOEs) was 2.5% in the ponatinib arm and 1.2% in the imatinib arm. Adjusted for differences in exposure, the rates were 2.7 and 2.1 per 100 patient years, respectively. Two events in the ponatinib arm led to treatment discontinuation.

The rate of venous thromboembolic events (VTEs) was 11.7% in the ponatinib arm and 12.3% in the imatinib arm. The exposure-adjusted rates were 14.0 in the ponatinib arm and 22.4 in the imatinib arm. Three participants (1.8%) in the ponatinib arm two participants (2.5%) in the imatinib arm had serious VTE events.

The rates of discontinuations due to an AE were 10.4% and 8.6% in the ponatinib and imatinib arms, respectively. The rates of dose interruptions were 68.1% and 39.5%, respectively. The difference may partly be due to dose modification guidelines being more conservative in the Study Protocol and in the prescribing information for ponatinib than in the prescribing information for imatinib.

Deaths due to AEs were reported for 4.9% of patients in each arm. None of the deaths in the ponatinib arm and one in the imatinib arm was considered related to treatment.

3.5. Uncertainties and limitations about unfavourable effects

The safety population is relatively limited (n=163 and n=81 in the ponatinib and imatinib arms of PhALLCON, respectively), and the study is still ongoing. The currently presented data from PhALLCON is from the data cutoff 12 August 2022. At this timepoint, there were still 41.5% of subjects on treatment in the ponatinib arm. To allow a better characterisation of the safety of the new treatment regimen in the proposed target population, updated data on AOEs and VTEs from a later data cutoff should be provided when available post-approval.

3.6. Effects Table

Table 38. Effects Table for ponatinib in combination with chemotherapy in adult patients with newly diagnosed Ph+ ALL (data cut-off: 12 August 2022)

Effect	Short description	Unit	Ponatinib (N=154)	Imatinib (N=78)	Uncertainties / Strength of evidence	References
Favourable Effects						
MRD-neg CR	MRD-negative CR at the end of induction	% (n/N)	34.4 (53/154)	16.7 (13/78)	Primary endpoint, statistically significant.	PhALLCON study
	Risk difference (95% CR)		0.18 (0.06,0.29)			
	p-value		0.0021		EFS data inconclusive but showing a positive trend.	
Unfavourable Effects						
Arterial occlusive events	Absolute rate	%	2.5%	1.2%		PhALLCON CSR
	Exposure-adjusted rate	Per 100 PY	2.7	2.1		"
venous thromboembolic events	Absolute rate	%	11.7%	12.3%		"
	Exposure-adjusted rate	Per 100 PY	14.0	22.4		"
Myelosuppression (grouped term)	All grades Grade 3-4	%	82.8% 40.5%	87.7% 54.3%		"
Infections and Infestations	All grades Grade 3-4	%	70.6% 30.7%	55.6% 24.7%		"
Haemorrhage (grouped term)	All grades Grade 3-4	%	27.6% 1.8%	29.6% 7.4%		
Gastrointestinal disorders		%	81.0%	80.2%		"
Hepatotoxicity (grouped term)	All grades Grade 3-4	%	64.4% 28.2%	56.8% 13.6%		"

Effect	Short description	Unit	Ponatinib (N=154)	Imatinib (N=78)	Uncertainties / Strength of evidence	References
Pancreatitis (grouped term)	Clinical Chemical	%	3.7% 29.4%	3.1% 37.0%		"

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Ponatinib as a first-line therapy, in combination with reduced-intensity chemotherapy, demonstrated a statistically significant improvement in the primary endpoint of MRD-negative CR rate at end of induction in participants with newly diagnosed Ph+ ALL. This is accompanied by a trend towards increased EFS. However, the latter is not nominally statistically significant.

The pivotal PhALLCON study has a substitution design where patients are randomised to standard of care imatinib or test agent ponatinib, as add-on to reduced intensity chemotherapy. Imatinib is approved for this use. The addition of imatinib to chemotherapy increases the rate of complete remissions and was shown to increase EFS and OS compared to chemotherapy alone, based on historical comparisons (Glivec SmPc, section 5.1.) Both imatinib and ponatinib provide antitumoral action by occupying the ATP-binding site of BCR-ABL1. Thus, they share the same fundamental mechanism of action.

The increase in MRD-negativity with ponatinib demonstrates that this regimen provides more antitumoral activity than does imatinib. This indicates that, given the similar mechanism of action, and provided that it is sufficiently tolerated, the impact of ponatinib on EFS is likely to be at least similar to that of imatinib, and possibly greater.

MRD-negativity is presently not understood as a metric that independently isolates clinical benefit, and therefore is not an established registrational endpoint in this setting. Moreover, this has not been established as a trial-level surrogate of time to progression or overall survival.

However, in the context of a study where ponatinib is investigated as a substitute for imatinib (a product with established clinical benefit in the treatment context), a conclusion can be made that the efficacy of ponatinib is not inferior to that of imatinib. Further, the difference in MRD-negativity that was seen supports the inference that ponatinib may provide longer EFS than imatinib. This inference is supported by available EFS data, although these in themselves are inconclusive.

The currently available data indicate that ponatinib + reduced-intensity chemotherapy has a comparably manageable safety profile and is tolerated to a similar degree as imatinib + reduced-intensity chemotherapy. Importantly, when adjusted for differences in treatment duration (longer on ponatinib, indicating reasonable tolerability), the rate of AOEs was not considerably higher in the ponatinib arm than in the imatinib arm.

As the available safety data do not allow sufficiently informed conclusions on the tolerability of ponatinib in combination with a more intense chemotherapy backbone than that administered in the pivotal study, PhALLCON, the indication is restricted to combination of ponatinib with reduced-intensity chemotherapy.

In summary, there is no concern that ponatinib would be less effective than the registered comparator, imatinib, and it may be superior. Moreover, the emerging safety profile indicates that the impact of AOE on relative B/R versus imatinib is not considerable, and that the safety profile is not substantially worse than the comparator.

On this basis, an approval based on MRD-negativity would be possible. The applicant has committed to providing the final EFS and OS data from the PhALLCON study as an Annex II condition (key to B/R) expected in December 2028.

3.7.2. Balance of benefits and risks

The benefit/risk of ponatinib in combination with reduced intensity chemotherapy for the treatment of adult patients with newly diagnosed Ph+ ALL is positive.

3.7.3. Additional considerations on the benefit-risk balance

The applicant has committed to provide the final EFS and OS data from the PhALLCON study as an Annex II condition.

3.8. Conclusions

The overall B/R of Iclusig is positive.

The following measures are considered necessary to address issues related to efficacy:

In order to confirm the efficacy and safety of Iclusig in combination with reduced-intensity chemotherapy in adult patients with newly diagnosed Ph+ ALL, the MAH should submit the final results of Ponatinib-3001 (PhALLCON) a randomized, active controlled, multicenter, open label trial (by 31 December 2028).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	II	I, II and IIIB

Extension of indication to include treatment in combination with reduced-intensity chemotherapy of adult patients with newly-diagnosed Ph+ ALL for ICLUSIG, based on interim results from study Ponatinib-3001 (PhALLCON); this is a phase 3, randomized, open-label, multicenter study comparing ponatinib versus imatinib, administered in combination with reduced intensity chemotherapy, in patients with newly diagnosed Ph+ ALL; supportive data were derived from two single-arm, open-label clinical studies (AP24534 11 001 in combination with chemotherapy and INCB 84344-201 as

monotherapy). As a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Annex II is also updated to include the commitment to provide the final study results of study Ponatinib-3001 (PhALLCON). Version 24.1 of the RMP has also been submitted. In addition, earlier approved updates were incorporated to the PI.

The variation leads to amendments to the annexes I, II and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

This recommendation is subject to the following new condition:

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

- **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.

In addition, 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.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
In order to confirm the efficacy and safety of Iclusig in combination with reduced-intensity chemotherapy in adult patients with newly diagnosed Ph+ ALL the MAH should submit the final results of Ponatinib-3001 (PhALLCON) a randomized, active controlled, multicenter, open label trial.	December 2028

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Iclusig is not similar to Blincyto, Besponsa, Kymriah and Tecartus within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Iclusig-H-C-2695-VR/0000263550’