EMA/CHMP/874113/2022
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Iclusig

International non-proprietary name: ponatinib

Procedure No. EMEA/H/C/002695/II/0064

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	13 Aug 2022	13 Aug 2022	☐
☐	CHMP Rapporteur Assessment Report	07 Oct 2022	07 Oct 2022	☐
☐	CHMP Co-Rapporteur Assessment Report	07 Oct 2022	n/a	☐
☐	PRAC Rapporteur Assessment Report	14 Oct 2022	14 Oct 2022	☐
☐	PRAC members comments	19 Oct 2022	n/a	☐
☐	CHMP Co-Rapporteur Critique	19 Oct 2022	17 Oct 2022	☐
☐	Updated PRAC Rapporteur Assessment Report	20 Oct 2022	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	27 Oct 2022	27 Oct 2022	☐
☐	CHMP members comments	28 Oct 2022	28 Oct 2022	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	03 Nov 2022	03 Nov 2022	☐
☐	Request for Supplementary Information	10 Nov 2022	10 Nov 2022	☒
☐	Start of procedure	26 Feb 2023	26 Feb 2023	☐
☐	CHMP Rapporteur Assessment Report	28 Mar 2023	28 Mar 2023	☐
☐	PRAC Rapporteur Assessment Report	31 Mar 2023	28 Mar 2023	☐
☐	PRAC members comments	04 Apr 2023	04 Apr 2023	☐
☐	Updated PRAC Rapporteur Assessment Report	05 Apr 2023	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	14 Apr 2023	14 Apr 2023	☐
☐	CHMP members comments	17 Apr 2023	17 Apr 2023	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 Apr 2023	20 Apr 2023	☐
☐	Request for Supplementary Information / Opinion	26 Apr 2023	26 Apr 2023	☐
☒	Letter of withdrawal from MAH	n/a	11 Aug 2023	☐

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List of abbreviations

Abbreviation	Definition
1L	first-line
ABL	Abelson
AE	adverse event
ALL	acute lymphoblastic leukemia
BCR	breakpoint cluster region
BCR-ABL	breakpoint cluster region-Abelson
BM	bone marrow
BMT	bone marrow transplantation
CCyR	complete cytogenetic response (abbreviated as CCgR in parts of the assessment)
CHR	complete hematologic response
CI	confidence interval
CML	chronic myeloid leukemia
CMR	complete molecular response (abbreviated as CMolR in parts of the assessment)
CNS	central nervous system
CR	complete response
CSR	Clinical Study Report
DFS	disease-free survival
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EMA	European Medicines Agency
EPAR	European public assessment report
ESMO	European Society for Medical Oncology
EU	European Union
FAS	full analysis set
GIMEMA	Gruppo Italiano Malattie EMatologiche dell'Adulto
HDT	high-dose therapy
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
hyper-CVAD	hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone
INCB84344	Ponatinib
ITC	indirect treatment comparison
ITT	intent-to-treat
KD	kinase domain
KM	Kaplan-Meier
MAIC	matching-adjusted indirect comparison
max	Maximum
MDACC	MD Anderson Cancer Center

min	Minimum
MMR	major molecular response
NA	not available
NCCN	National Comprehensive Cancer Network
ND	not determined
NE	not evaluable
NICE	National Institute for Health and Care Excellence
OR	odds ratio
ORR	overall response rate
OS	overall survival
PAIC	population-adjusted indirect comparison
PCyR	partial cytogenic response
Ph+	Philadelphia chromosome-positive
PI	principal investigator
PR	partial response
RT-qPCR	reverse transcription-quantitative polymerase chain reaction
SAP	Statistical Analysis Plan
SCT	stem cell transplantation
SLR	systematic literature review
STD	standard deviation
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TTE	time to event
US	United States
WBC	white blood cell
WHO	World Health Organization

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Incyte Biosciences Distribution B.V. submitted to the European Medicines Agency on 29 June 2022 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include treatment of newly diagnosed adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL), either with Iclusig (ponatinib) in combination with chemotherapy, or with Iclusig (ponatinib) monotherapy after corticosteroid induction in patients not eligible to receive chemotherapy-based regimens, based on final results from studies AP24534-11-001 and INCB 84344-201. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 22 of the RMP has also been submitted.

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

Information relating to orphan designation

Two conditions, for which ponatinib has received orphan medicinal product designations, are

covered by these indications:

• Treatment of chronic myeloid leukaemia (EU/3/09/716)

• Treatment of acute lymphoblastic leukaemia (EU/3/09/715)

The proposed extension to the currently approved indication is for "the treatment of adult patients with newly diagnosed Ph+ ALL". This intended indication is covered by the orphan medicinal product designation received for the treatment of acute lymphoblastic leukaemia (EU/3/09/715).

Information on paediatric requirements

At the time of submission of the application, a partial compliance check was completed by PDCO/EMA and adopted on 23/08/2019 in procedure EMEA-C1-001186-PIP01-11-M02. As detailed in the compliance report, the agreed PIP contains three studies which are not yet completed but have been deferred.

Therefore, no further PIP compliance check is required within the scope of this variation application.

Information relating to orphan market exclusivity

NA

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.

Protocol assistance

The MAH has not sought any Protocol assistance from the CHMP.

2. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
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Extension of indication to include treatment of newly diagnosed adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL), either with Iclusig (ponatinib) in combination with chemotherapy, or with Iclusig (ponatinib) monotherapy after corticosteroid induction in patients unfit for intensive chemotherapy and allogeneic stem cell transplant, based on final results from studies AP24534-11-001 and INCB 84344-201. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 22 of the RMP has also been submitted.

☐is recommended for approval.

☐is not recommended for approval.

☒is subject to a request for supplementary information (please refer to the RSI section and the proposed Changes to the Product Information in a separate document) before a recommendation can be made.

The responses timetable to the Request for Supplementary Information will be[1] [2]:

☐ 30 days (15 days to assess with clock-stop, 8 days to assess with immediate responses)

☒ 60 days (36 days to assess)

[1] Instructions to assessor: please select one of the two options. If no option is selected, a default 30-day assessment timetable will be applied.
[2] Note to MAH: this timetable refers to the assessment of the responses to the RSI and is determined by the Rapporteur/assessor; it does not refer to the clock-stop necessary for the preparation and submission of the responses which is determined by the MAH and communicated to the Procedure Assistant upon receipt of the assessment report.

3. Scientific discussion

3.1. Introduction

3.1.1. Problem statement

Disease or condition

Philadelphia chromosome–positive ALL (Ph+ ALL) is a rare malignancy of the blood and bone marrow. It is a malignant proliferation of lymphoid cells characterized by a translocation of chromosomes 9 and 22, leading to the fusion of the BCR coding sequence on chromosome 22 with the tyrosine kinase coding region of ABL1 of chromosome 9 (this translocation is referred to as the Philadelphia chromosome). The result is the expression of a BCR-ABL1 fusion oncoprotein with constitutive activation of ABL1 tyrosine kinase activity, which in turn activates cell signaling pathways that promote cell proliferation and survival.

Prior to the introduction of tyrosine kinase inhibitors (TKIs), the outcome of Ph+ ALL was poor, both in terms of achievement of complete response (CR) and long-term survival (Pullarkat et al 2008), and the only curative option was represented by allogeneic hematopoietic stem cell transplantation (HSCT). Treatment with chemotherapy alone resulted in CR of 45%-90%, but the median duration of CR was approximately 10 months, and most patients later relapsed, leading to few long-term survivors (Faderl et al 2000, Liu-Dumlao et al 2012, Ravandi and Kebriaei 2009).

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

State the claimed the therapeutic indication

Iclusig is indicated in newly diagnosed adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL)

- in combination with chemotherapy
- as monotherapy after corticosteroid induction in patients not eligible to receive chemotherapy-based regimens

After the first round, the proposed monotherapy indication has been amended as follows: "with corticosteroid induction in patients unfit for intensive chemotherapy and allogeneic stem cell transplant"

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 by that a rare disease. Predisposing risk factors for adult ALL are not known (ESMO guideline 2016).

Biologic features, aetiology and pathogenesis

ALL consists of a clonal expansion of malignant blasts that are atypical lymphoid cells originating from B- or T-lymphocyte precursor cells. The malignant blasts harbour morphologic, immunophenotypic and cytogenetic/genetic features that are the basis for classification and contribute to the identification of high-risk subsets. In Ph+ ALL, the malignant cells express BCR-ABL1 fusion oncoprotein with constitutive activation of ABL1 tyrosine kinase activity.

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 mutation (in 2 different alleles) or compound mutation (2 mutations in the same allele) in BCR-ABL1 (Zabriskie et al 2014). According to the MAH, some of these mutations may be resistant to all available TKIs (Bauer et al 2013, Khorashad et al 2013, Shah et al 2007, Soveriniet al 2021, Zabriskie et al 2014).

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). According to the MAH, front-line treatment with ponatinib (rather than treatment with first- or second-generation TKIs followed by ponatinib) may achieve deeper and more durable responses, and reduce the emergence of resistant mutations (Chiaretti and Foà 2015, Rousselot et al 2016, Bauer et al 2013, Khorashad et al 2013, Shah et al 2007, Soverini et al 2021, Zabriskie et al 2014).

Clinical presentation, diagnosis and prognosis

Clinical ALL risk groups are defined by several disease-related and some host-related factors. In addition, the individual prognosis is highly refined by ALL response dynamics (ESMO guidelines 2016), see Table 1.

Table 1 High-risk factors in adult ALL according to ESMO guidelines 2016

High-risk factors in adult ALL

Risk factors	Risk subsets (notes)	Recommendations
Patient-related		
– Age (years)	– >40/55/65	Mandatory
– Performance status (ECOG score)	– >1	Highly recommended
Disease-related		
– WBC ($\times 10^9$/l)	– >30 (B-lineage)/>100 (T-lineage)	Mandatory
– Immunophenotype (B-T-subsets)	– Pro-B/early and mature-T	Mandatory
– Cytogenetics (karyotype)	– Ph+/t(4;11)+/other adverse	Mandatory
– Genetics	– BCR-ABL1+/MLL+/PBX-E2A+/	Mandatory
	Ph-like/IKZF1del/ETP/unmutated NOTCH1	Recommended for new clinical trials
– Miscellaneous	– Central nervous system involvement	Mandatory
Response dynamics		
– corticosteroid sensitivity (blast count after pre-phase)	– Poor prednisone response ($\geq 1 \times 10^9$/l)	Recommended
– early blast cell response (BM morphology)	– Day 8–15 blasts ≥5%	Recommended
– time to CR (no. of courses)	– >1 cycle (late CR)	Mandatory
– MRD (molecular/LAIP)	– MRD+ (post-induction)	Mandatory

ALL, acute lymphoblastic leukaemia; ECOG, Eastern Cooperative Oncology Group; WBC, white blood cells; Ph+, Philadelphia-positive; Ph, Philadelphia; ETP, early T-cell precursor; BM, bone marrow; CR, complete remission; MRD, minimal residual disease; LAIP, leukaemia-associated immunophenotype.

Ph+ ALL, with a constitutive activation of ABL1 tyrosine kinase, is considered to be an intermediate/high-risk ALL subset even after the introduction of TKI treatment (ESMO guidelines 2016).

Management

Treatment

As a brief overview, treatment for newly diagnosed ALL patients often consist of a pre-phase followed by induction, consolidation/transplant, and then maintenance phase, see Figure 1.

Figure 1 Diagnosis and risk assessment in adult ALL for achievement of CR and risk-oriented post-remission therapy according to ESMO guidelines 2016.

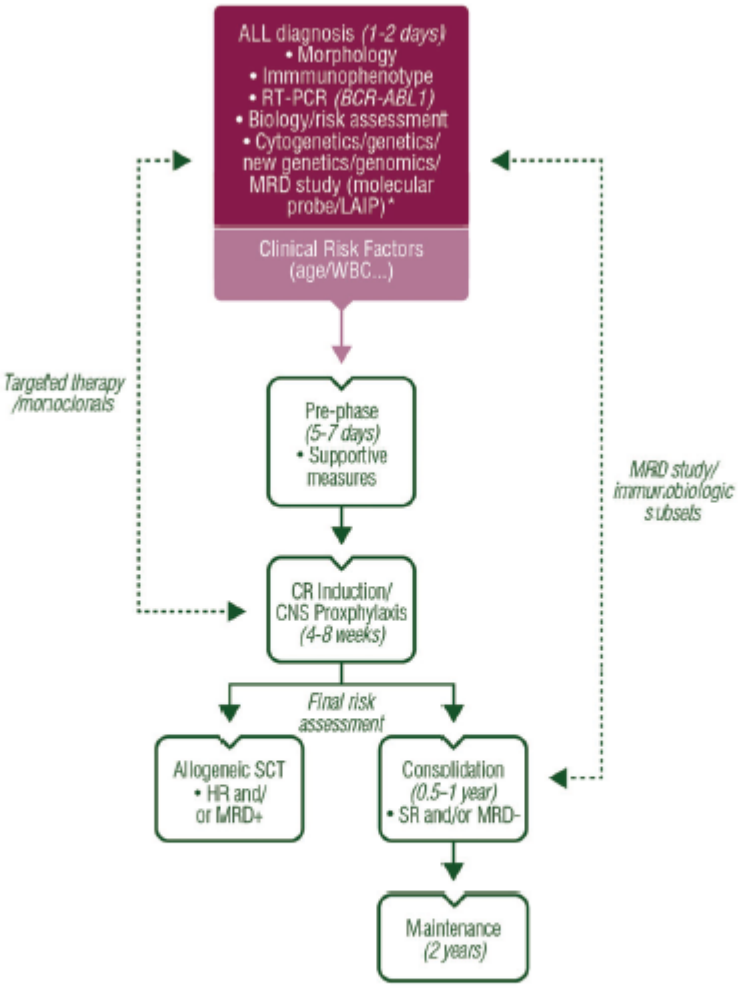


Figure 1. Diagnosis and risk assessment in adult ALL for achievement of CR and risk-oriented post-remission therapy. Major diagnostic subsets are identified within 1–2 days to allow start of pre-phase therapy, identify cases eligible to targeted therapy (TKI in Ph+ ALL), and set up the MRD study. Pre-phase therapy allows for management/prevention of metabolic/infectious/haemorrhagic complications before start of induction therapy, and checks HLA identity between patient and siblings. Induction/early consolidation therapy (incorporating CNS prophylaxis) aims to induce CR with a deep MRD response, to support subsequent risk- and MRD-oriented therapy with/without allogeneic SCT. ALL, acute lymphoblastic leukaemia; RT-PCR, reverse transcriptase polymerase chain reaction; MRD, minimal residual disease; LAIP, leukaemia-associated immunophenotype; WBC, white blood cells; CR, complete remission; CNS, central nervous system; SR, standard risk; HR, high risk; SCT, stem-cell transplantation; TKI, tyrosine kinase inhibitor; Ph+, Philadelphia-positive; HLA, human leucocyte antigen.

For patients with Ph+ ALL, the NCCN guidelines (NCCN 2021) recommend treatment within a clinical trial as a first choice. If that is not possible, 1L treatment with a TKI is recommended, along with chemotherapy and/or a steroid. In older patients, the NCCN guidelines recommend either reduced-intensity chemotherapy or no chemotherapy (steroid only) in combination with a TKI. Similarly, ESMO guidelines recommends that a TKI should be administered continuously and should be combined with chemotherapy in front-line therapy, see Table 2. Central nervous system prophylaxis is also recommended to be administered throughout treatment.

Table 2 Recommendations for TKI/chemotherapy combinations in adult Ph+ ALL according to ESMO guidelines 2016

Recommendations for TKI/chemotherapy combinations in adults with Ph+ ALL	
	Recommendation
Adults with Ph+ ALL should be treated front line with a combination of imatinib or second-generation TKI and chemotherapy.	Mandatory
Reduced-intensity chemotherapy may be used in combination with TKI during the first treatment cycles, to minimise early toxicity and mortality.	Recommended
TKI should be administered as continuously as possible, with respect to haematological tolerance.	Recommended
There is no standard post-remission treatment in patients not receiving allogeneic SCT because of no donor or advanced age. Prolonged administration of imatinib/consolidation chemotherapy followed by imatinib maintenance should be applied.	Recommended
Allogeneic SCT in first CR with a standard myeloablative conditioning probably remains the best post-remission option in younger patients with a donor. The role of reduced-intensity conditioning allogeneic SCT remains to be evaluated in this ALL subset.	Recommended
Post-SCT imatinib maintenance is recommended for 1–2 years of duration.	Recommended
Prolonged monitoring of *BCR-ABL1* MRD levels is recommended, associated with resistance mutation screening in patients with persistent MRD detection or re-increasing MRD levels. Results should be used to guide the switch towards a second- or third-generation TKI in these higher risk patients.	Recommended

TKI, tyrosine kinase inhibitor; Ph+, Philadelphia-positive; ALL, acute lymphoblastic leukaemia; SCT, stem-cell transplantation; CR, complete remission; MRD, minimal residual disease.

HSCT is performed in some patients, depending on factors such as availability of a suitable donor and the suitability of the patient to withstand the procedure. HSCT, however, is an option for a limited number of patients and is associated with mortality and relapse (Liu-Dumlao et al 2012).

Unmet medical need

In patients aged 18 to 59 years with newly diagnosed Ph+ ALL, rates of complete molecular response (CMR) with imatinib plus either vincristine and dexamethasone or hyper-CVAD were similar (22.6% and 28.6%, respectively, after 2 cycles), and estimated 5-year EFS and OS tended to be higher in combination with hyper-CVAD (5-year EFS: 42.2% vs 32.1%; 5-year OS: 48.3% vs 43.0%; Chalandon et al 2015).

Dasatinib with vincristine and dexamethasone as 1L therapy in patients aged ≥ 55 years with newly diagnosed Ph+ ALL showed a CR rate of 96%, a 5-year EFS rate of 27%, and a 5-year OS rate of 36% (Rousselot et al 2016).

As described above, patients may develop resistant mutations in BCR-ABL1 when they present with relapsed or refractory Ph+ ALL after 1L treatment with first- or second-generation TKIs (Zabriskie et al 2014). The MAH states that there is an unmet medical need for novel treatment options that can suppress the development of mutations and lead to long-term clinical benefit and thus prevent sequencing multiple intensive treatments including HSCT with associated mortality (Styczyński et al 2020, Warraich et al 2020).

Assessor's comment:

An unmet medical need in the target population can be agreed.

In response to RSI, with regard to ponatinib and the unmet need, the MAH argues that 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, and that long-term disease control in newly diagnosed Ph+ ALL has been challenging particularly due to the emergence of T315I mutations.

Due to the low number of patients with mutation tests performed at baseline and during follow-up and relapse in the two presented studies, most "evidence" is indirectly drawn conclusions. However, the comparably few documented relapses e.g in Study INCB 84344-201, may indicate a potential favourable action of ponatinib with regard to suppression of resistance mutations.

3.1.2. About the product

Ponatinib is a third-generation TKI inhibitor that inhibits aberrant downstream signaling of native BCR-ABL1 and its variants, and by that promote apoptosis in BCR-ABL1–positive cells (O'Hare et al 2009). Ponatinib was designed to inhibit mutant forms of the BCR-ABL1 protein that cause resistance to other TKIs, including the T315I gatekeeper mutation that confers resistance to other BCR-ABL1 inhibitors such as first-generation TKI imatinib and second-generation TKI dasatinib. The T315I mutation is the most common mutation associated with resistance to both imatinib and dasatinib (Chiaretti and Foà 2015, Rousselot et al 2016).

According to the MAH, through its multikinase inhibitor activity (Huang et al 2010), ponatinib is able to suppress mutations and control the genomic instability that can activate other oncogenic routes or promote the emergence of other mutations in advanced disease (Calabretta and Perrotti 2004, Johansson et al 2002).

Ponatinib is currently approved in 56 countries, including the US, Canada, Japan, and the EU. Ponatinib originally received accelerated approval in the US on 14 DEC 2012. Ponatinib received full approval in the EU on 01 JUL 2013 and in the US in 28 NOV 2016.

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

- chronic phase, accelerated phase, or blast phase CML who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation
- Philadelphia chromosome-positive ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

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

For information regarding orphan designation, please refer to "Information relating to orphan designation" in section 1.

On 27 March 2018 the MAH sought MHRA scientific advice on clinical and regulatory aspects of ponatinib treatment of (i) newly diagnosed Ph+ ALL in combination with chemotherapy and (ii) newly diagnosed Ph+ ALL not eligible for chemotherapy in combination with corticosteroids,

ref:1782/Ponatinib. The MHRA did not agree that the results of the two investigator sponsored trials could support the proposed indication extension, due to limitations of the studies including exploratory nature, non-comparative design, concerns regarding the study integrity, and a small number of patients. Further, justification for the proposed dosage was requested since dose modification due to concerns regarding vascular events was performed in a protocol amendment.

On 24 April 2018 the MAH sought MPA scientific advice on frontline Iclusig studies in PH+ ALL, MPA reference number 4.2.3-2018-009500. The MPA had then considered the advice given by MHRA one month earlier. The MPA requested a re-analysis of the 2 studies after data cleaning. Challenges regarding single-arm design, small sample size, missing data, a potential effect of patient selection, and a single-center effect for the trial completely performed at MD Anderson Cancer Center (Study AP24534-11-001) was pointed out. MPA recommended an in-depth review of the patient characteristics at inclusion, and compare them with historical data, to address potential bias. Further, MPA requested detailed data on response maintenance after dose reduction and a rationale for reducing/not reducing the dose, together with a discussion on the impact of early ponatinib use with regard to the risk of vascular adverse effects. The company was also asked to discuss the potential pharmacokinetic and pharmacodynamics interactions when ponatinib is administered with chemotherapy and address the extrapolation from HCVAD chemotherapy (used in the is study AP24534-11-001) to other chemotherapy backbones. In addition, MPA underlined the need to justify the positioning of ponatinib in 1L vs 2L. A follow-up advice after data re-analysis was recommended.

On 18 November 2020 the MAH sought MPA (rapporteur) scientific advice on frontline Iclusig in Ph+ ALL after an update of the results from the 2 initially investigator sponsored studies. This scientific advice addressed questions to each of the studies (INCB84344-201 and AP24534-11-001) as described below. Overall, MPA commented that it is yet unclear that the clinical benefit outweighs the safety risk for an earlier line indication. Further, the MPA pointed out that the two single-arm studies cannot isolate the treatment effect of ponatinib, however, this may be addressed conducting historical comparison analysis. Further, subgroup analysis to identify the presence or emergence of mutations, outcome for patients with CNS disease and description of patients who underwent SCT is expected. Also, a follow-up rapporteur pre-submission interaction was encouraged to align on eventual filing approach in the event of multiple variations occurring in the same timefrmame.

AP24534-11-001

The MAH will be expected to justify the contribution of Iclusig by external comparison. The importance of external validity of the data and the relationship of the study population to the proposed indication was reiterated. Extrapolation discussion from the HCVAD chemotherapy backbone used in this study to the chemotherapy backbone commonly used in Europe would need to be part of the dossier. A detailed data analysis of the different dosing regimens pre/post amendment (45mg initial starting dose period vs dose reductions post amendment) and their relevance to intended patient population and outcome will be required.

INCB84344-201

A submission was recommended to include historical comparison of responses reached vs steroids/background therapy only. The dossier would need to address how the obtained efficacy results, including durability of response, outweighs the risks for use of the product in the intended patient population. Further, external validity and definition of "non-eligibility" to chemotherapy were identified as key issues to be addressed in a submission dossier.

On 30 June 2021 a presubmission meeting with MPA was held. MPA commented that the challenges with the single-arm design in the two studies will be an assessment issue. MPA suggested the wording "in combination with chemotherapy" instead of *"integrated with chemotherapy"* for the indication with

combination of ponatinib and hyper-CVAD. Further, MPA requested a justification and discussion why the extrapolation from hyper-CVAD to any chemotherapy regimen is appropriate. For the monotherapy indication, MPA commented that corticosteroid induction should be reflected in SmPC section 4.1 and also requested an associated guidance about corticosteroid induction section 4.2. In addition, a justification of the safety profile of the combinations versus chemotherapy or corticosteroids alone was requested, to discuss any differences in type of events or severity compared to chemotherapy or corticosteroids.

Assessor's comment:

The MAH has taken a part of the recommendations given by MPA into consideration;

- As requested, description of participants who had CNS disease at baseline, and participants who received SCT post-study therapy were presented in both studies.
- Analysis of BCR-ABL1 kinase domain mutations were planned but not performed following the transfer of study sponsorship from GIMEMA to Incyte in study INCB84344-201, mutation results are presented for three participants.
- Indication wording was modified according to given advice for both indications.

However, the following recommendations are not considered fulfilled in the application;

- Address how historical comparison analysis may isolate the treatment effect of ponatinib in the study design with single-arm studies.
- Justification of proposed dosage.

3.1.4. General comments on compliance with GCP

The MAH claims that the clinical trials were performed in accordance with GCP. However, due to the several protocol amendments and unclarities about study conduct in both pivotal trials, GCP inspections are mandated and a request for GCP inspection has been adopted. Satisfactory outcome of these inspections will be necessary for the efficacy data appraisal and for an ultimate decision on the approvability of the new indication. The outcome of this inspection and the satisfactory responses to its findings are part of the responses to the Request for Supplementary Information and will be needed by Day 91.

3.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

3.2.1. Ecotoxicity/environmental risk assessment

The MAH provided a Phase I ERA resulting in a $PEC_{surfacewater}$ of 0.00495 µg/l which is below the action limit of 0.01 µg/l. According to this the ERA can stop in Phase I. This is considered acceptable.

However, no data on the n-octanol/water partition coefficient (log Kow) have been submitted. According to the EMA guideline on the environmental risk assessment of medicinal products for human use, the submission of data on log Kow is part of a Phase I ERA to allow for a PBT screening. Hence, in order to complete the Phase I ERA, information on the log Kow of ponatinib should be provided in accordance with the Q&A document by the European Medicines Agency (EMA) Questions and answers

on 'Guideline on the environmental risk assessment of medicinal products for human use' (EMA/CHMP/SWP/44609/2010). The log Kow should be determined experimentally. Studies performed in accordance with OECD Test Guidelines are preferred. A calculated value is generally not acceptable.

Assessor's comment:

The MAH provided information on the determination of the log Kow of ponatinib HCl using the slow stirring method. This is acceptable. The log Kow was determined to be 4.5 at pH 7 which meets the criterium for a PBT assessment. As for PBT assessment, the MAH refers to the original ERA which was limited to a discussion of biodegradability and toxicity based on cited data (from IBACON project). In the original ERA, it was concluded that ponatinib was not readily biodegradable. According to the ERA guideline, substances that are not readily biodegradable require further investigation of fate in a water sediment system. However, no such data were reported.

The outcome of the toxicity assessment was misinterpreted in the original ERA. Hence, contrary to the conclusion by the MAH, the NOEC for ponatinib fulfils the criterium for toxicity according to ECHA guideline.

There were no data on bioaccumulation included in the original ERA**.** Moreover, the study reports for the cited biodegradability and toxicity studies were not submitted. Hence, the PBT assessment does not fulfil the requirements in the EMA guideline on ERA.

The MAH is therefore requested to submit a step-wise PBT/vPvB assessment in accordance with the CHMP guideline on ERA, including the required studies compliant with relevant OECD Guidelines (e.g., OECD TG308 for persistence assessment, followed by OECD TG305 for bioconcentration assessment). If such studies are not immediately available, the MAH should provide a planned submission date (preferably within two years). In addition, the MAH is requested to provide the reports for any cited references used (e.g., aquatic toxicity studies)..

3.3. Clinical aspects

3.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. However, due to the several protocol amendments and unclarities about study conduct in both pivotal trials, GCP inspections are mandated.

3.3.2. Pharmacokinetics

No new pharmacokinetic data available, pharmacokinetic sampling has not been performed in the pivotal clinical trials.

Assessor's comment:

In general, it is preferred to collect PK samples when studies in new indications are performed, to confirm that pharmacokinetics is similar between indications and to be able to investigate e g the relationship between PK and efficacy and/or safety or to study potential drug-drug interactions. This has not been done. This may be acceptable based on available efficacy and safety data, and the

unlikelihood of clinically relevant interactions with cytostatics. The exception is methotrexate (see below)

Pharmacokinetic interaction studies

No pharmacokinetic interaction studies have been performed. The MAH has discussed the potential for pharmacokinetic interactions between ponatininb and the corticosteroids and chemotherapy drugs used in the clinical studies.

The MAH concludes that overall, DDI potentials between ponatinib and corticosteroids and chemotherapy drugs used in Study AP24534-11-001 and Study INCB 84344-201 (hyper-CVAD and high-dose MTX and cytarabine) are considered low and are not expected to have any clinically meaningful impact on the efficacy and safety of ponatinib when used in combination.

According to the SmPC ponatinib is neither an inhibitor or inducer of CYP enzymes. In vitro data however suggests inhibition of Pgp and BCRP.

Ponatinib is cleared by CYP3A4 metabolism, and none of the cytotoxic drugs included in the studies are known as strong CYP3A4 inhibitors and inducers.

The MAH has also presented the protein binding of all components and concluded that the risk of displacement interactions is low.

Assessor´s comment

The MAH has provided a mechanistic discussion regarding potential pharmacokinetic interactions between the components of the drug combinations. No clinical pharmacokinetic data is available, as no PK samples were taken in the studies, and there are no dedicated DDI studies between the agents. This can be acceptable, as clinical efficacy and safety data is available with the applied combinations, so potential risks or benefits with changes in the PK of the individual components have been covered with clinical data.

It is agreed with the MAH that ponatinib is not a perpetrator of CYP interactions. The MAH has however not discussed the fact that ponatinib is a Pgp and BCRP inhibitor in vitro, and many of the cytotoxic drugs are substrates of these transporters. Pgp inhibition in vitro is however only seen at higher ponatinib concentrations corresponding to levels that are evident in the gastrointestinal tract during absorption. As the cytotoxic drugs are given intravenously there should not be a risk for Pgp inhibition in this case.

BCRP inhibition has however been seen at substantially lower concentrations in vitro, and methotrexate is mentioned in the Iclusig SmPC as an example of a drug where there may be a risk for increased side effect when combined with ponatinib. The MAH has not discussed the risk for increased MTX toxicity in the current proposed drug combination with ponatinib. For further discussion of the safety of this combination and the MTX dose, please refer to section 3.5.7.

Ponatinib is a CYP3A4 substrate, but the observed effect of a strong inhibitor and inducer, respectively, is modest. It is thus agreed that no dramatic effects of the concomitant drug (e g corticosteroids that may be weak or moderate inducers) on the plasma exposure of ponatinib are expected.

3.4. Clinical efficacy

3.4.1. Dose response studies

According to the MAH, analyses from earlier phase 1/2 trials of ponatinib indicated that a dose-effect relationship exists with the occurrence of responses. Administration of 45 mg ponatinib resulted in achievable concentrations above the 40 nM threshold concentration; a concentration that is sufficient to inhibit viability of cells expressing all BCR-ABL1 mutants tested (by >90%), including T315I, and suppressed the emergence of any mutant clones in a preclinical mutagenesis assay. The results of multivariate analyses suggested that higher dose intensities in refractory patients yield higher response rates across the dose range tested. This provided the basis for evaluating a starting dose of 45 mg once daily.

Thus, based on the safety, pharmacokinetics, and response observations available at the time of study initiation, including the MTD defined in the Phase 1 trial AP24534-07-101, the 45 mg dose was chosen as the recommended dose for use in theses phase 2 clinical trials, which was also consistent with the approved starting dose.

Assessor's comment:

No formal dose-response studies have been carried out for the applied 1L Ph+ ALL indications. Instead, the MAH suggests the already approved starting dose of ponatinib (45 mg once daily) in the current application. The same starting dose of ponatinib is suggested in both combination with chemotherapy and as monotherapy in more frail patients. The rationale for the starting dose provided by the MAH is acknowledged.

3.4.2. Main studies

Two Phase 2 studies assess the efficacy and safety of ponatinib as 1L treatment in patients with Ph+ ALL to support the proposed indication, see Table 3.

Table 3 Overview of the two pivotal studies of ponatinib as 1L therapy in Ph+ ALL

Protocol Number	Phase	Protocol Title	Patient Population	Ponatinib Dosing	Status
AP24534-11-001 (MDACC 2011-0030) www.clinicaltrials.gov NCT01424982	2	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 (acute phase or blast phase) that was either previously untreated or previously treated with 1-2 cycles of chemotherapy with or without other TKIs	45 mg daily on Days 1-14 of the first course of treatment, with dose reduction to 30 mg for subsequent courses or to 15 mg after CHR[a]	Ongoing
INCB 84344-201 (GIMEMA LAL1811) www.clinicaltrials.gov NCT01641107 EudraCT 2012-002761-35	2	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 2 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	45 mg daily	Completed

ALL = acute lymphoblastic leukemia; BCR-ABL = breakpoint cluster region-Abelson; CHR = complete hematologic response; CML = chronic myeloid leukemia; hyper-CVAD = hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; GIMEMA = Gruppo Italiano Malattie EMatologiche dell'Adulto; MDACC = MD Anderson Cancer Center; Ph+ = Philadelphia chromosome-positive; SCT = stem cell transplantation; TKI = tyrosine kinase inhibitor.
Note: Data cutoff date of 14 DEC 2020 for Study AP24534-11-001 and 30 SEP 2021 for Study INCB 84344-201.
[a] Dose reduction was initiated after Protocol Amendment 2.

Source Summary of Clinical Efficacy section 1.4

3.4.2.1. Study AP24534-11-001 - ponatinib as add-on to Hyper-CVAD chemotherapy backbone

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.

3.4.2.1.1. Methods

Study participants

Patients were selected from those referred to the leukemia department at MDACC through the normal of process of referral.

Key eligibility criteria

- Had a diagnosis of one of the following:
  - Previously untreated Ph+ ALL [either t(9;22) and/or BCR-ABL1 positive] (included patients initiated on first course of hyper-CVAD before cytogenetics known) or with lymphoid accelerated or blast phase CML.
  - Previously treated Ph+ ALL or CML (in accelerated phase or blast phase), after 1 to 2 courses of chemotherapy with or without other TKIs:
    - If they had achieved CR, they were assessable only for EFS and OS, or
    - If they had failed to achieve CR, they were assessable for CR, EFS, and OS.
- ≥18 years old.
- (ECOG) performance status ≤ 2.
- Adequate liver function as defined by the following criteria:
  - Total serum bilirubin <1.5× upper limit of normal (ULN), unless due to Gilbert's syndrome.
  - Alanine aminotransferase (ALT) <2×ULN.
  - Aspartate aminotransferase (AST) <2.5×ULN.
- Adequate pancreatic function as defined by the following criteria:
  - Serum lipase and amylase <1.5×ULN.
- Adequate cardiac function as assessed clinically by history and physical examination.

Key exclusion criteria

- History of acute pancreatitis within 1 year of study or history of chronic pancreatitis.
- History of alcohol abuse.
- Uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL).
- Clinically significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to:
  - Any history of MI, stroke, or revascularization.
  - Unstable angina or transient ischemic attack prior to enrollment.
  - Congestive heart failure within 6 months prior to enrollment or left ventricular ejection fraction (LVEF) less than lower limit of normal per local institutional standards within 6 months prior to enrollment.
  - Diagnosed or suspected congenital long QT syndrome.
  - Any history of clinically significant atrial or ventricular arrhythmias (such as atrial fibrillation, ventricular tachycardia, ventricular fibrillation, or Torsade's de Pointes) as determined by the treating physician.
  - Prolonged QTc interval on pre-entry electrocardiogram (ECG) (>470 msec) unless corrected after electrolyte replacement.

- Any history of venous thromboembolism (VTE) including deep venous thrombosis or pulmonary embolism.
- Uncontrolled hypertension (diastolic blood pressure >90 mmHg; systolic >140 mmHg).

- Taking any medications or herbal supplements that were known to be strong inhibitors of CYP3A4 within at least 14 days before the first dose of ponatinib.
- Prior history of treatment with ponatinib for >1 month. Patients who had been treated with ponatinib for 1 month prior to starting the treatment were eligible.
- History of significant bleeding disorder unrelated to cancer, including:
  - Diagnosed congenital bleeding disorders (eg, von Willebrand's disease).
  - Diagnosed acquired bleeding disorder within one year (eg, acquired anti-factor VIII antibodies).

Assessor's comment:

The key eligibility criteria did not only include previously untreated Ph+ ALL, but also previously untreated lymphoid CML in accelerated or blast phase. Eighty six of the 87 participants enrolled in Study AP24534 11 001 had been diagnosed with Ph+ ALL and one participant had been diagnosed with CML transforming into lymphoid blast phase.

Not only previously untreated patients were included in this study, since prior treatment with 1 to 2 courses of chemotherapy with or without other TKIs was allowed at study entry.

Treatments

Patients received ponatinib in combination with 8 cycles of chemotherapy study treatment (each lasting 21 days), alternating between 2 drug combinations:

Hyper-CVAD (for Cycles 1, 3, 5, and 7) consisted of

- 300 mg/m² of cyclophosphamide intravenously over 2 to 3 hours every 12 hours for 6 doses on days 1 to 3
- a continuous daily infusion of sodium mercaptoethanesulfonate at 600 mg/m² per day for 24 hours starting 1 hour before cyclophosphamide and completed approximately 12 hours after the final cyclophosphamide dose
- doxorubicin intravenously at 50 mg/m² over 24 hours on day 4
- 2 mg of vincristine intravenously on days 1 and 11
- and 40 mg of dexamethasone intravenously and orally on days 1 to 4 and days 11 to 14.

High-dose methotrexate and cytarabine (for Cycles 2, 4, 6, and 8) consisted of

- methotrexate intravenously at 200 mg/m² over 2 hours, followed by 800 mg/m² over 22 hours on day 1
- cytarabine intravenously at 3 g/m² over 3 hours every 12 hours for 4 doses on days 1 to
- and 50 mg of citrovorum rescue intravenously or orally, followed by 15 mg every 6 hours for 8 doses beginning 12 hours after methotrexate completion.

Ponatinib was given orally at 45 mg per day for the first 14 days of Cycle 1 then continuously at 45 mg per day for the subsequent cycles. However, after 37 patients were treated, the protocol was amended

to reduce the dose of ponatinib to 30 mg per day at Cycle 2, with further reduction to 15 mg once a CMR (defined as absence of quantifiable BCR-ABL1 transcripts with a sensitivity of 0.01%) was achieved.

Rituximab was to be administered intravenously at 375 mg/m² during the first 4 cycles in patients with CD20 expression of at least 20% of leukemic cells.

For central nervous system (CNS) prophylaxis, intrathecal methotrexate and cytarabine was to be given alternately on Days 2 and 7 of Cycles 1 to 6 for a total of 12 doses.

The treatment period was followed by approximately 24 months of maintenance chemotherapy with monthly cycles of IV vincristine on Day 1 (2 mg intravenously), oral prednisone (200 mg) on Days 1 to 5, and daily ponatinib at 30 mg in patients with no CMR and at 15 mg in those with CMR. Months 6 and 13 of maintenance were intensification cycles of hyper-CVAD and ponatinib. Patients with CMR or who were poor candidates for such intensification, or both, were to continue maintenance therapy uninterrupted at the discretion of the treating physician. Patients could discontinue the intensive chemotherapy in Cycle 1-8 and move to the maintenance phase prior to completion of 8 cycles of chemotherapy (or for transitional treatment prior to allogeneic bone marrow transplant) if intolerant after discussion with the PI.

After the maintenance period, per investigator discretion if patients were benefitting from therapy, continued daily ponatinib was permitted.

Assessor's comment:

The 37 first patients were treated with 45 mg of ponatinib day 1-14 in Cycle 1-8, but, the dose of ponatinib was reduced to 30 mg in Cycle 2 to 8 following Protocol amendment due to concerns about cardiovascular toxicity, and upon achievement of CMR ponatinib could be further reduced to 15 mg daily. The MAH is asked to reinstate the original posology of ponatinib during the first cycle in SmPC section 4.2, i.e, 14 days ponatinib treatment.

The treatment period was followed by 24 months of maintenance chemotherapy with monthly cycles of vincristine and prednisone, in combination with daily ponatinib at 30 mg in patients with no CMR and at 15 mg in those with CMR. Months 6 and 13 of maintenance were intensification cycles of hyper-CVAD and ponatinib administered. Patients with CMR or not candidates for such intensification could abstain the intensification cycles. Also, patients were allowed to discontinue the intensive chemotherapy during Cycle 1-8 and move to the maintenance phase prior to completion of 8 cycles of chemotherapy.

The MAH reports that 64 participants (74%) did not complete 8 cycles of chemotherapy in the study, 43 participants (49%) did not receive intensification cycles during the maintenance phase, and 40 participants (46%) stopped maintenance therapy at or before 24 months of maintenance phase treatment. To reflect the given treatment and inform prescribers that a considerable portion of the patients continued to maintenance therapy without completing 8 cycles of hyper-CVAD/MTX plus cytarabine, the MAH should specify in SmPC section 5.1 that only 26% of the patients completed the induction treatment but that also those who discontinued chemotherapy before completion of eight cycles were allowed to enter the maintenance therapy.

After the maintenance period, per investigator discretion if patients were benefitting from therapy, continued daily ponatinib was permitted. The MAH needs to justify the recommendation in SmPC section 4.2 which states that discontinuing ponatinib should be considered if a complete haematologic response has not occurred by 3 months, since this timeframe was not studied in Study AP24534-11-001.

Further, clarification in SmPC section 5.1 regarding reasons for discontinuation is requested.

In addition to ponatinib and Hyper-CVAD, also intrathecal CNS prophylaxis was to be administered, and CNS directed treatment was given to patients with CNS disease at baseline. The MAH has added somewhat excessive information on given CNS prophylaxis or treatment in SmPC section 5.1, which could be shortened.

However, no information on given rituximab can be found in the SmPC. It is considered necessary to clarify the use of rituximab, to adequately reflect the given treatment. The MAH should describe the use of rituximab in SmPC section 5.1, and preferably also add a statement in section 4.2 that treatment with anti-CD20 in CD20+ patients should follow standard clinical guidelines.

Objectives and endpoints

Primary endpoint was EFS at 2 years. EFS was defined as the time from the first day of treatment until any failure (resistant disease, relapse, or death).

Secondary endpoints were overall response rate (ORR), OS, and safety.

Assessor's comment:

Considering the fact that a majority of Ph+ ALL patients are expected to reach a complete hematologic remission after first line treatment, EFS at two years is in principle an endpoint that captures clinical benefit in the present treatment scenario.

While it is recognised that EFS at two years without treatment would be close to 0 in the absence of therapy, the study is a single-arm trial with add-on design. Therefore, neither this nor any other endpoint is capable of isolating the effect of ponatinib over and above hyper-CVAD in the pivotal trial. This is a fundamental deficiency which was pointed out in scientific advice.

The secondary endpoints, ORR and OS, are clinically meaningful. However, OS is a time dependent endpoint that does not isolate drug effects in a single-arm trial. Thus, OS data should be removed from SmPC section 5.1.

The analyses of efficacy measures are descriptive, and no formal statistical tests were performed for efficacy endpoints, which is appropriate in this setting.

Sample size

No statistical considerations for the sample size calculation were performed in this investigator-sponsored trial.

According to the study protocol, in a previous study (unpublished; N = 139) on the combined data from hyper-CVAD plus imatinib or dasatinib, the 2-year EFS was 0.49 years (95% confidence interval [CI]: 0.4 to 0.58). The goal of the current trial was to achieve a 2-year EFS rate >50% (ie, median EFS >24 months). Initially, the study was expected to accrue a maximum of 60 patients, with referral pattern of 20-25 patients/year (accrual completed in 30 - 36 months), with an additional 24 months of follow-up.

Assessor's comment:

The MAH´s goal (or, rather the sponsor's) with the current trial was to achieve a 2-year EFS rate >50%, in view of a historical reference 2-year EFS rate 0.49, from unpublished data, on the combination of hyper-CVAD plus imatinib or dasatinib.

The sample size, in the present study, was not based on any statistical considerations. Rather, it appears to have been estimated from an expected referral pattern and what may have been considered a reasonable study timeframe.

Initially up to 3 years recruitment with an additional follow-up of 24 months should have implied a total study duration of approximately 5 years. The first patient was enrolled in 2011, hence study AP24534-11-001 could have been expected to have completed in 2016, instead, the sample size was amended. Upon request, the MAH clarified that the rationale for the increased sample size from 60 to 100 participants from protocol version 16 February 2016 was to provide a more robust set of data and a more comprehensive safety profile.

The dataset that underlies the outcome presentations in the submitted CSR comprise a total of 87 subjects. At the time of the current data cut-off (14 December 2020), it was stated that there were no patients remaining on study treatment. The MAH clarified that there had been no selection of subjects and that N=87 represented all subjects (with newly diagnosed Ph+ ALL) that had been enrolled at the 14 DEC 2020 data cut-off date. The MAH also admitted that they erroneously described that there were no patients in the current dataset remaining on study treatment.

The sample size in the submitted dossier (n=87) is limited and posed, and still poses, an uncertainty in terms of interpretation of results, including external validity and the possibility to validly compare with any external data.

Randomisation and Blinding (masking)

This was a single-arm open-label study.

Statistical methods

According to CSR section 6.2, the statistical analysis plan (SAP) was prepared post-data cut, but prior to the receipt of patient-level data, in response to an FDA request to submit a CSR to support the cutaneous T-cell lymphoma indication for a supplemental biologics license application submission.

One SAP is submitted which is specified as; final version 1.0, dated 15 June 2020, based on protocol version No. 34 with protocol date 06 April 2020. The data cut-off date for the analyses presented in the current CSR occurred after the finalization of the SAP (14 December 2020).

It is specified in the SAP that analysis of efficacy measures will be descriptive in this study, and no formal statistical tests will be performed for efficacy endpoints.

Analysis population

There was one analysis population for the study; the enrolled population noted in the datasets included all patients enrolled in the study (n = 87) and for whom BCR-ABL1^{IS} could be measured (ie, patients who have the b2a2/b3a2 transcript type), regardless of whether they received the assigned study drug. The primary analysis of molecular efficacy was based on this population. Patients with the b2a2/b3a2 transcript type without response assessments were considered as non-responders in the primary efficacy analysis. The enrolled population is referred to as the safety population in the CSR data tables and listings.

Definitions and analysis of selected endpoints

EFS (primary endpoint): time from the first day of treatment until any failure (resistant disease, relapse, or death).

OS (secondary endpoint): time from the first day of treatment to time of death from any cause. OS was calculated from the time of treatment initiation until death from any cause.

The primary analysis of the primary endpoint, EFS, was based on the following criteria for response:

- Complete Response (CR): ≤5% blasts in normocellular or hypercellular bone marrow, and with ≥1 × 10^9/L granulocytes and ≥100 × 10^9/L platelets in the peripheral blood.
- Molecular CR (CMR): Same as for CR with RT-PCR negativity for BCR-ABL1 or with RT-PCR for BCR-ABL with 4 log reduction from baseline and/or ≤0.01%.
- Partial Response (PR): As above for CR except for the presence of 6% to 25% marrow blasts.
- Overall response rate (ORR) is defined as the percentage of patients achieving complete remission and partial remission

In addition, major molecular response (MMR) was defined as BCR-ABL1 transcripts less than 0.1% by the international scale for patients with p210 transcripts and a 3-log reduction from baseline for patients withp190 transcripts, but not meeting criteria for CMR.

Survival rates at specific time points and response rates were calculated along with 95% confidence intervals. Survival curves were plotted by the Kaplan-Meier method.

The number and percentage of patient received SCT will be summarized.

For the patients who have received stem cell transplant, the disease or death status will be continuously collected post-transplant, and the primary analysis of EFS will ignore censoring at the time of transplant. However, a sensitivity analysis for EFS may be conducted by censoring patients at the time of transplant.

Subgroup analyses may be performed for efficacy endpoints, as appropriate.

Assessor's comment:

It is in general crucial that the SAP is finalised before any analyses are performed. This is of even more importance in open-labelled studies and in this respect, it should be noted that this a single-centre study. The SAP describing the analysis presented in the current CSR was prepared post data cut-off after the performance of analyses as laid out in the protocol. However, it should be acknowledged that the origin of an SAP authored by the MAH was regulatory advice (e.g., MPA, April 24, 2018, and, as stated by the MAH, apparently also the FDA). The submitted SAP, version: Final 1.0, is dated 15 June 2020: more than two years later than having met with the MPA. The MAH confirmed that the SAP was signed off in JUN 2020 and clarified that no patients' data for primary endpoint were available at the time of the finalisation of the SAP: the data cut-off date for the analysis was 14 DEC 2020, Takeda received baseline data on 06 AUG 2020 while the remaining data were received by 11 FEB 2021.

Upon request, the MAH further explained that there were no data-driven elements implemented in the SAP. The main differences between the SAP and the study protocol version 26 were, as highlighted by the MAH, more primary endpoint (EFS) analysis details.

Also, it was specified that the SAP was based on protocol version No. 34. However, the last submitted protocol version is No. 26. The MAH clarified that the SAP was drafted based on Protocol v.26, misnumbered as v.34.

The many protocol amendments are of concern and cannot be considered anything else, but data driven given the open-label single-arm and single-centre design. In addition, analyses have been performed during the study and "preliminary" study outcomes have been published.

In total 26 versions of the protocol have been submitted and major changes have been highlighted in the CSR. Transparency is however questioned in that the actual changes within each amendment cannot be comprehended unless the versions are compared side by side. In addition, the rational for the changes appears to be lacking.

Study outcomes will be assessed as outlined in the SAP prepared by the MAH provided the SAP does not imply changes contradictory to how the study was initially planned. However, study conduct is a major concern that is considered to hamper the interpretation of study outcomes.

According to the SAP in protocol version 1, a Bayesian time-to-event (TTE) monitoring method was to be implemented to perform futility monitoring continuously throughout the trial that was to be stopped early if it was found very unlikely that the experimental therapy yielded better EFS than that of previous trials in similar setting. The pre-defined rule (probability (Pr) (QE > QS | data) <0.085) was to be applied continuously, with the probability criterion recomputed based on the most recent data available after each EFS event observed. It has been acknowledged in the CSR that an early stopping rule was in place for the study if the EFS was ever likely to be less than the historical 2-year event-free survival of 49% but that no stopping rules were met. Interim analyses for futility are generally accepted. Of more concern is the multiple analyses that preceded the current and for which outcomes have been published.

Efficacy measures was descriptive in this study, and no formal statistical testing were planned or have been performed. This approach is agreed given the study design and its obvious exploratory nature.

Contrary SAP wording, the CSR stated that survival curves were plotted and compared using a log rank test and that differences in subgroups by different covariates were evaluated with the χ^2 test for nominal values and the Mann-Whitney U and Fisher's exact tests for continuous variables. In a

single-arm setting, p-values are of less use in the interpretation of outcomes. It will however be expected that results are presented using 95% CIs.

Allogeneic stem cell transplantation was not censored for any survival estimates in the primary EFS analysis. The primary approach could be accepted, the planned sensitivity analysis using censoring is supported. However, in the end it has been reported that only 2 patients went to transplant.

3.4.2.1.2. Results

Participant flow

The analysis population in this study is titled the enrolled population and is referred to as the safety population in the CSR data tables and listings.

Table 4 Overall participant Disposition

Table 4: Study AP24534-11-001 Overall Participant Disposition

	Total (N = 87) n (%)
Safety population	87 (100.0)
Reason participant discontinued treatment	42 (48.3)
Complete withdrawal/revocation by PI	1 (2.4)
Complete withdrawal/revocation by participant	4 (9.5)
Death	10 (23.8)
Lost to follow-up	3 (7.1)
Toxicity/side effects/complications	3 (7.1)
Treatment completed per protocol	11 (26.2)
Other[a]	10 (23.8)
Number of participants who went to transplant	2 (2.3)
Categories of death reason	20 (23.0)
Cardiac event	4 (20.0)
Multi organ failure/sepsis	4 (20.0)
Other	12 (60.0)
Summary of participants still on treatment	0
Summary of participants in long-term follow-up	45 (51.7)

CSR = Clinical Study Report; PI = principal investigator; SCT = stem cell transplantation.
Note: The enrolled (safety) population is considered the same as the enrollment population.
Note: Percentages are calculated out of the number of the enrolled (safety) population.
Note: The denominator of each subgroup percent is the row of category total number.
Note: Data cutoff date of 14 DEC 2020.
[a] Two participants were terminated from the study for SCT, 8 participants were terminated to move to an umbrella, long-term follow-up study for participants completing therapy on Department of Leukemia protocols.
Source: AP24532-11-001 CSR Table 15.1.2.

Source Summary of Clinical Efficacy section 2.1.5.1

Assessor's comment:

The MAH has stated that 24 participants were actually continuing to receive treatment at the time for data cut-off (14 December 2020), which is not presented in the current Overall participant Disposition in Table 4. Thus, the MAH is asked to present an updated and correct table for Participant disposition in study AP24534-11-001.

Recruitment

Study period: The first subject signed informed consent form 17 November 2011. At the time of data cut-off (14 December 2020), there were no patients on study treatment and 45 patients (51.7%) remained in the long-term follow-up phase. Data are presented from study initiation until the data cut-off date.

Study center: MDACC.

Assessor's comment:

The MAH needs to justify the external validity of the generated data with regard to the relationship between the study population and the proposed target population from this single-center study.

Conduct of the study

Protocol Amendments

In total, 26 different protocol versions are submitted. Below is a summary of Major Changes in selected protocol versions, from CSR section 9.7.1:

Version 3, 10 Aug 2011;

- Removed relapsed patients from inclusion in the study.

Version 5, 11 Apr 2012;

- Increased the dose of cytarabine for patients age ≥60 years from 0.5 g/m2 to 1 g/m2.

Version 8, 14 Oct 2013;

- Added new exclusion criterion: "Patients with history of pulmonary embolism."
- Decreased the dose of ponatinib given in courses 2 through 8 from 45 mg PO daily to 30 mg PO daily.
- Decreased dose of ponatinib in maintenance therapy with vincristine and steroids from 45 mg to 30 mg PO daily as tolerated. Also decreased the dose of ponatinib in intensifications interrupting maintenance phase in months 6 and 13 from 45 mg PO daily to 30 mg PO daily.
- Added the option to further decrease the dose of ponatinib from 30 mg to 15 mg daily if needed due to toxicity.
- Clarified that rituximab "may be added" for patients with CD20 expression.

Version 9, 20 Feb 2014;

- Updated Inclusion Criterion 7 to add additional criteria for excluding patients with clinically significant, uncontrolled, or active CV disease
- Added the following text:
  - Section 4.2:
    - "Patients should receive treatment with a statin, as prophylaxis against arterial thrombotic events, if not contraindicated. Atorvastatin, 10-20 mg per day, is suggested

Version 12, 18 Jul 2014;

- Decreased the dose of ponatinib "to 15 mg once CMR is achieved unless judged necessary to stay on 30 mg and after discussion with the PI."

Version 13, 1 Aug 2014;

- Added an eighth cycle of ponatinib to be given continuously without interruptions unless due to toxicity.

Version 16, 9 Feb 2016;

- Maximum expected sample size was changed from 60 to 100 patients.

Version 18, 7 March 2017;

- Added that "patients may be enrolled after having received 1-2 courses of hyper-CVAD from an outside facility (this treatment is known to be standard of care)." And that "patients will receive a total 8 cycles of induction and consolidation with hyper-CVAD regardless of whether the patient had received prior chemotherapy at home or not [chemotherapy with hyper-CVAD given at home will be counted as part of the 8 cycles])."
- Added that ponatinib may be continued indefinitely at the current dose if felt in the best interest of the patient.

Version 20, 28 Aug 2018;

- Added the inclusion of patients with lymphoid accelerated or blast phase CML.

Version 23, 13 May 2019;

- Added a list of clinical scenarios where it would be acceptable to vary the administration of chemotherapy regimens.

Version 24, 8 Aug 2019

- Decreased dose of methotrexate from "200 mg/m^2 IV over 2 hrs (+ 1 hour) followed by 800 mg/m^2 over 22 hrs on Day 1" to "150 mg/m^2 IV over 2 hrs (+ 1 hour) followed by 600 mg/m^2 over 22 hrs on Day 1."
- Decreased dose of cytarabine from "3 g/m^2 IV over 3 hrs" to "2 g/m^2 IV over 3 hrs." Removed "If age >60 years: reduce methotrexate to 25% (250 mg/m^2) and cytarabine to 1 g/m^2 over 3 hours every 12 hours for 4 doses."

Version 25, 20 Sep 2019;

- Added that modification may be made when necessary on a case-by-case basis after discussion with the principal investigator. This would not be considered a protocol deviation.

Version 26, 06 Apr 2020;

- Revised the definition of molecular CR to read: "Same as for CR with RT-PCR negativity for BCR-ABL1. or with RT-PCR for BCR-ABL1 with 4 log reduction from baseline and/or ≤0.01%.

Protocol deviations

Significant protocol deviations, defined as those involving inclusion or exclusion criteria or primary endpoint assessments, are summarized in Table 5.

There were 9 significant protocol deviations, including treatment/procedure deviations (n = 5), patient failure to take all ponatinib doses as instructed, patient and site medication errors, failure to take study drug for insurance non-coverage, and informed consent deviations of missing witness signature and failure to document the informed consent process.

Table 5 Significant protocol deviations (Table 10.b)

Table 10.b Significant Protocol Deviations

	Hyper-CVAD + Ponatinib N = 87 n (%)
Subjects With At Least One Significant Protocol Deviation	8 (9.2)
Adverse Events	1 (1.1)
Eligibility	1 (1.1)
Informed Consent	2 (2.3)
Treatment/Procedures	5 (5.7)

Source: Table 15.1.3.

Note: Subject may be counted in more than one category of protocol deviations.

Source CSR section 10.2

Assessor's comment:

The numerous protocol amendments were, and are still, a concern and as in any open-label study cannot be considered anything else, but data driven. In addition, analyses have been performed during the study and "preliminary" study outcomes have been published.

Overall, study integrity and internal validity was questioned given that 26 different protocol versions were submitted in this dossier from an open label investigator-sponsored, single-centre, single-arm trial, with what appeared to be further protocol versions up to number 34, initially mentioned as the basis for the SAP, but now explained to have been an error. Furthermore, it was also noted that protocol version 15 does not exist in the submitted dossier. This was however never pursued.

From protocol version 24, the doses of methotrexate and cytarabine were reduced. The MAH has clarified that, overall, the study participants received methotrexate and cytarabine according to the original Protocol which is also described in SmPC section 5.1. In addition, there is now a recommendation for the management of chemotherapy related toxicity in SmPC section 4.2 and 4.4.

Baseline data

An overall summary of baseline characteristics in the safety population (which is the predefined analysis population for this study and represent the same population as the "enrolled population") is presented in Table 6.

Table 6 Demographics and baseline characteristics in the safety population (Table 5)

Table 5: Study AP24534-11-001 Demographics and Baseline Characteristics

	Total (N = 87)
Median age in years (range)	46.0 (21-80)
Sex, n (%)	
Male	44 (50.6)
Female	43 (49.4)
Race, n (%)	
Asian	5 (5.7)
Black or African American	6 (6.9)
White	64 (73.6)
Unknown	12 (13.8)
ECOG score, n (%)	
0	22 (25.3)
1	54 (62.1)
2	11 (12.6)
CNS disease, n (%)	
Yes	6 (6.9)
No	81 (93.1)
CD20-positive, n (%)	
Yes	21 (24.1)
No	66 (75.9)
BCR-ABL1 transcript, n (%)	
p190	63 (72.4)
p210	22 (25.3)
Missing	2 (2.3)
Cytogenetics, n (%)[a]	
Diploid	20 (23.0)
Ph+	67 (77.0)

BCR-ABL1 = breakpoint cluster region-Abelson 1; CNS = central nervous system; CSR = Clinical Study Report; ECOG = Eastern Cooperative Oncology Group; Ph+ = Philadelphia chromosome-positive.
Note: Data cutoff date of 14 DEC 2020.

Source Summary of Clinical Efficacy 2.1.5.2

Prior treatment

- Twenty-one participants had prior lines of therapy. Of these 21 participants, 15 participants received chemotherapy in combination with TKIs (dasatinib or imatinib) and/or rituximab, 4

participants received chemotherapy alone or with rituximab, 1 participant received imatinib and steroids, and 1 participant received dexamethasone and dasatinib.

Assessor's comment:

At baseline, the median age was 46.0 years (range: 21-80 years), most participants (87.4%) had an ECOG score of 0-1, gender was balanced, and 73.6% of the participants were White. The majority of the patients (93.1) were free of CNS disease and the majority (75.9%) were CD20 negative. The majority of patients (72.4%) had the P190 BCR-ABL1 transcript.

Among the 21 participants who had received antileukemic therapy before study entry, 18 were in CR at the time of enrolment. These 18 patients were only assessable for EFS and OS evaluations, but not for CR evaluation.

Numbers analysed

The predefined analysis population for this study is the enrolled population (n=87), which is referred to as the safety population in tables.

Outcomes and estimation (data cut-off date of 14 DEC 2020)

Primary Efficacy endpoint – EFS at 2 years

Median duration of follow-up for EFS in all enrolled participants was 47.10 months (95% CI: 37.7, 70.7).

Table 7 EFS analysis (safety population) (Table 6)

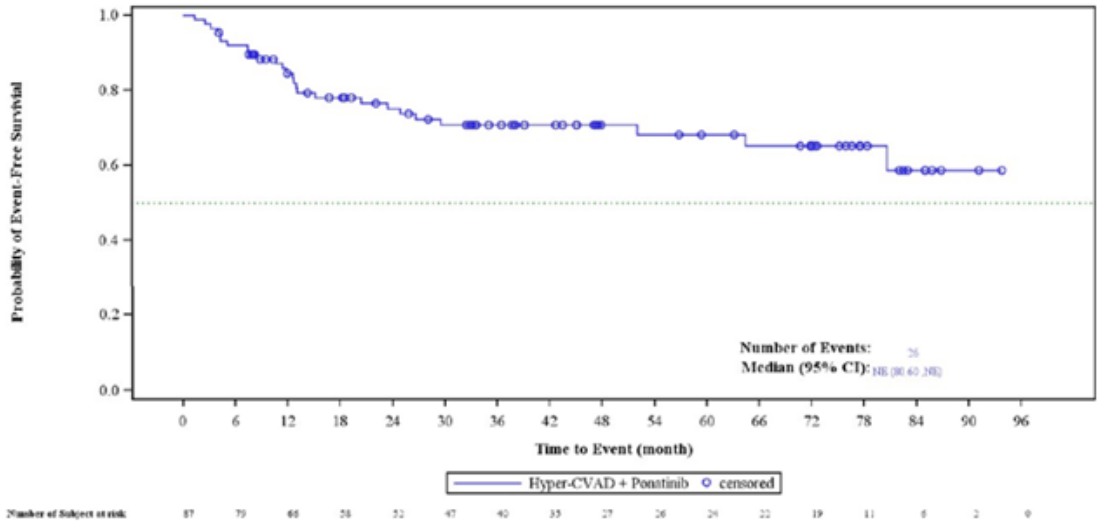
Table 6: Study AP24534-11-001 Analysis of Event-Free Survival (Safety Population)

	Total (N = 87)
Number of participants with events, n (%)	26 (29.9)
Number of participants censored, n (%)	61 (70.1)
EFS (months)	
25th percentile (95% CI)	24.90 (11.90, 80.60)
Median (95% CI)	NE (80.60, NE)
75th percentile (95% CI)	NE (NE, NE)
Min, max	1.40, 93.80[a]
KM estimates (95% CI) [no. at risk]	
12 months %	84.5 (74.8, 90.7) [n = 66]
24 months %	75.1 (64.0, 83.2) [n = 52]
36 months %	70.7 (59.1, 79.6) [n = 40]
60 months %	68.1 (55.7, 77.7) [n = 24]

CI = confidence interval; CSR = Clinical Study Report; EFS = event-free survival; KM = Kaplan-Meier; max = maximum; min = minimum; NE = not evaluable.
Note: Event-free survival is defined as from the first dose date until death due to any cause or relapse.
Note: Data cutoff date of 14 DEC 2020.
[a] This participant (duration 93.80 months) was censored.

Source Summary of Clinical Efficacy 2.1.6.1

Figure 2 Kaplan-Meier plot of EFS (safety population)



CI = confidence interval; CSR = Clinical Study Report; hyper-CVAD = hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; NE = not evaluable.
Note: Data cutoff date of 14 DEC 2020.

Source Summary of Clinical Efficacy 2.1.6.1

Subgroup analyses of EFS

Subgroup analysis of EFS by disease characteristics at baseline showed similar EFS rates based on the presence of CNS disease at baseline (n=6, Table 8). Numerically higher EFS rates were observed for CD20 negative (n=66) versus CD20 positive (n=21) patients, Table 9. For patients with p190 BCR-ABL1 transcript at baseline (n=63), the 2-year Kaplan-Meier estimated EFS rate was 69%. For patients with p210 BCR-ABL1 transcript at baseline (n=22), the 2-year Kaplan-Meier estimated EFS rate was 90%, see Table 11.

Table 8 EFS in patients with CNS disease at baseline

Table 15.2.1.7
Analysis of Event-Free Survival (EFS) by Disease Characteristics
Safety Population

CNS Disease = Yes

	Hyper-CVAD + Ponatinib (N=6)
Kaplan-Meier Estimates (95% CI) [No. at risk]	
0 Months % (95% CI)	100 (100 , 100)[n= 6]
6 Months % (95% CI)	83.3 (27.3, 97.5)[n= 5]
12 Months % (95% CI)	83.3 (27.3, 97.5)[n= 4]
18 Months % (95% CI)	83.3 (27.3, 97.5)[n= 4]
24 Months % (95% CI)	83.3 (27.3, 97.5)[n= 4]
30 Months % (95% CI)	62.5 (14.2, 89.3)[n= 3]
36 Months % (95% CI)	62.5 (14.2, 89.3)[n= 2]
42 Months % (95% CI)	62.5 (14.2, 89.3)[n= 2]
48 Months % (95% CI)	62.5 (14.2, 89.3)[n= 2]
54 Months % (95% CI)	62.5 (14.2, 89.3)[n= 2]
60 Months % (95% CI)	62.5 (14.2, 89.3)[n= 2]

Source CSR Table 15.2.1.7

Twenty one participants (24%) were deemed CD20+ at baseline among the enrolled population of 87 participants. These CD20+ participants received a median of 4 cycles of rituximab (range: 2-6 cycles).

The analysis of EFS by CD20 positivity at baseline from which results should be interpreted with caution due to the low number of participants in the group with baseline CD20+ (n = 21), and the obvious difficulties with sorting out the prognostic versus predictive nature of CD20 positivity in this setting.

Table 9 EFS in patients with CD20 negative and CD20 positive disease at baseline

Variables	Hyper-CVAD + Ponatinib (N = 87)	
	CD20+ (n = 21)	CD20– (n = 66)
No. of participants with events	8 (38.1)	18 (27.3)
No. of participants censored	3 (61.9)	48 (72.7)
Median (95% CI)	80.60 (10.70, NE)	NE (64.40, NE)
KM estimates at 24 months, % (95% CI) [no. at risk]	71.1 (46.6, 85.9) [n = 13]	76.2 (63.0, 85.2) [n = 39]

Source: AP24534-11-001 CSR Table 15.2.1.7.

Table 10 EFS in patients with BCR-ABL1 transcript=P190 at baseline

Table 15.2.1.7
Analysis of Event-Free Survival (EFS) by Disease Characteristics
Safety Population

BCR-ABL1 Transcript = P190

	Hyper-CVAD + Ponatinib (N=63)
Kaplan-Meier Estimates (95% CI) [No. at risk]	
0 Months % (95% CI)	100 (100 , 100) [n=63]
6 Months % (95% CI)	90.4 (79.9, 95.6) [n=56]
12 Months % (95% CI)	80.1 (67.6, 88.2) [n=45]
18 Months % (95% CI)	73.0 (59.7, 82.5) [n=40]
24 Months % (95% CI)	69.0 (55.2, 79.3) [n=34]
30 Months % (95% CI)	67.0 (53.0, 77.6) [n=31]
36 Months % (95% CI)	67.0 (53.0, 77.6) [n=27]
42 Months % (95% CI)	67.0 (53.0, 77.6) [n=24]
48 Months % (95% CI)	67.0 (53.0, 77.6) [n=20]
54 Months % (95% CI)	63.6 (48.7, 75.2) [n=19]
60 Months % (95% CI)	63.6 (48.7, 75.2) [n=17]

Source CSR Table 15.2.1.7

Table 11 EFS in patients with BCR-ABL1 transcript=P210 at baseline

Table 15.2.1.7
Analysis of Event-Free Survival (EFS) by Disease Characteristics
Safety Population

BCR-ABL1 Transcript = P210

	Hyper-CVAD + Ponatinib (N=22)
Kaplan-Meier Estimates (95% CI) [No. at risk]	
0 Months % (95% CI)	100 (100 , 100) [n=22]
6 Months % (95% CI)	95.5 (71.9, 99.3) [n=21]
12 Months % (95% CI)	95.5 (71.9, 99.3) [n=19]
18 Months % (95% CI)	90.2 (65.9, 97.5) [n=17]
24 Months % (95% CI)	90.2 (65.9, 97.5) [n=17]
30 Months % (95% CI)	79.5 (54.1, 91.8) [n=15]
36 Months % (95% CI)	79.5 (54.1, 91.8) [n=12]
42 Months % (95% CI)	79.5 (54.1, 91.8) [n=11]
48 Months % (95% CI)	79.5 (54.1, 91.8) [n= 7]
54 Months % (95% CI)	79.5 (54.1, 91.8) [n= 7]
60 Months % (95% CI)	79.5 (54.1, 91.8) [n= 7]

Source CSR Table 15.2.1.7

Two participants received HSCT and were terminated from the study. One participant who received HSCT was alive at last assessment (11 APR 2018), 1 participant died from sepsis and multi-organ failure after allogeneic HSCT (20 AUG 2013).

Mutations in the BCR-ABL1 KD were not reported.

Secondary Efficacy endpoints

ORR/CR

All 87 participants had a CR, including 18 participants that had a CR at baseline (these participants were assessable for EFS and OS only, but not CR). Of the 18 participants who had CR at the start of the study, all had received prior lines of therapy; 15 had received chemotherapy in combination with TKIs (dasatinib or imatinib) and 3 received either imatinib with steroids, chemotherapy alone, or dexamethasone with dasatinib.

The majority of participants had an MMR (88.4%) and a CMR was reported in 78.3% of participants. Complete cytogenetic response (CCyR) was not reported.

Table 12 Analysis of Overall response (Table 7)

Table 7: Study AP24534-11-001 Analysis of Overall Response (Safety Population)

	Total (N = 87)
CR, n (%)	
n	87
Yes	87 (100.0)[a]
No	0
MMR, n (%)	
n	69[b]
Yes	61 (88.4)
No	8 (11.6)
CMR, n (%)	
n	69[b]
Yes	54 (78.3)
No	15 (21.7)

CMR = complete molecular response; CR = complete response; CSR = Clinical Study Report; MMR = major molecular response.
Note: Data cutoff date of 14 DEC 2020.
[a] Complete response at baseline n = 18.
[b] Total excludes participants who had CR at baseline.

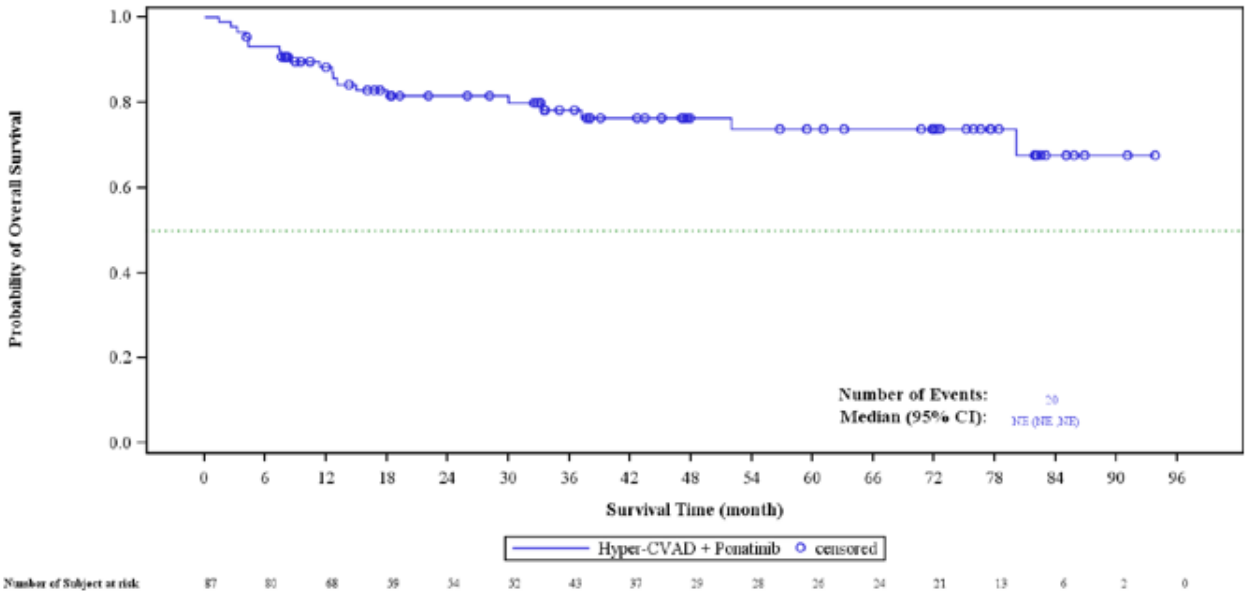
Source Summary of Clinical Efficacy 2.1.6.2.1

OS

With a median duration of follow-up for OS of 45.1 months (95% CI: 36.50, 63.10), the median OS was NE (80.10, NE). Most participants (77.0%) were alive at last contact. The number of participants with events was 20 (23.0%). The KM plot of OS for the safety population is presented in Figure 3.

Figure 3 Kaplan-Meier plot OS (safety population)

Figure 2: Study AP24534-11-001 Kaplan-Meier Plot for Overall Survival (Safety Population)



CI = confidence interval; CSR = Clinical Study Report; hyper-CVAD = hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; NE = not evaluable.
Note: Data cutoff date of 14 DEC 2020.

Source Summary of Clinical Efficacy 2.1.6.2.2

Assessor's comment:

Primary endpoint

According to the MAH, the goal of the current trial was to achieve a 2-year EFS rate >50% (ie, median EFS >24 months). As a background reference, the MAH refers to a previous study (unpublished; N = 139) on the combination of hyper-CVAD plus imatinib or dasatinib, with a 2-year EFS of 0.49 (95% confidence interval [CI]: 0.4 to 0.58).

Based on a data cut-off of 14 DEC 2020 with a median duration of follow-up for EFS of 47 months, 26 patients (29.9%) had an event, the median EFS was not reached, and the 2-year Kaplan-Meier estimated EFS rate (primary endpoint) was 75.1% (95% CI 64.0, 83.2).

The 5-year EFS rate was 68.1%. Similar EFS rates were observed in patients with CNS disease (n=6) as for those without CNS disease.

These endpoints and outcomes are indicative of clinically relevant efficacy; however, they do not isolate an effect of ponatinib, and the external validity of this small single-center study may be questioned. It is recognised, however, that before the introduction of TKIs in Ph+ ALL treatment, remission rates of 45%-90% with short median durations of responses in the range of approximately 10 months were achieved, with chemotherapy alone (Faderl et al 2000, Liu-Dumlao et al 2012, Ravandi and Kebriaei 2009). In patients aged 18 to 59 years with newly diagnosed Ph+ ALL, treatment with hyper-CVAD plus imatinib resulted in estimated 5-year EFS of 42.2% (Chalandon et al 2015).

The MAH is asked to discuss and justify to what extent the contribution of Iclusig to chemotherapy can be quantified in this setting with a single-arm trial, add-on trial in which Iclusig was given in combination with intensive chemotherapy.

Further, the MAH is asked to justify the external validity of the generated data and the relationship between the study population and the proposed target population, the discussion should cover the issue that the data submitted reports a single-center case series.

Secondary endpoints

All 87 participants reached a CR (secondary endpoint) at any time. Of note, 18 of 21 the participants that had received 1-2 cycles of prior treatment showed a CR already at baseline.

The 5-year OS rate was 73.8%. However, OS is a time dependent endpoint that does not isolate drug effects in a single-arm trial. OS data should, therefore, be removed from SmPC section 5.1.

Summary of main study(ies)

The following table summarises the efficacy results from the main study, of combination of hyper-CVAD and ponatinib, supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13. Summary of efficacy for trial AP24534-11-001

Title: 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)	
Study identifier	www.clinicaltrials.gov NCT01424982, MDACC 2011-0030
Design	Single-arm, open-label, single-center MDACC

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		8 cycles of Hyper-CVAD + ponatinib, followed by 24 months maintenance period. Not applicable Ponatinib continued indefinitely as appropriate at dose per investigator discretion if in the best interest of the patient.
Hypothesis	Exploratory: The MAH´s goal was to achieve a 2-year EFS rate >50%.		
Treatments group	Single-arm study, including Ph+ ALL and CML patients.		Hyper-CVAD x 8 in combination with ponatinib 45 mg per day for 14 days of cycle 1, then continuously (after protocol amendments) 30 mg per day from cycle 2, with further reduction to 15 mg once a CMR. A 24 months ponatinib maintenance period including recurrent chemo-treatments.
Endpoints and definitions	Primary: Event-free survival at 2 years	EFS at 2 years	EFS was defined as the time from the first day of treatment until any failure (resistant disease, relapse, or death).
	Secondary: Overall response rate	ORR	Percentage of patients achieving complete remission and partial remission.
Database lock	Data cut-off of 14 December 2020		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	The analysis population is the enrolled population (n=87), of which 86 patients had Ph+ ALL and 1 patient had CML transforming into lymphoid blast phase.	
Descriptive statistics and estimate variability	Treatment group	Ph+ ALL and Ph+ CML
	Number of subject	87
	EFS at 2 years, %	75.1
	(95% CI)	(64.0, 83.2)
	ORR, % (n)	100 (87)
Notes	The analyses of efficacy measures are descriptive, and no formal statistical tests were performed.	

3.4.2.2. Study INCB 84344-201 – monotherapy ponatinib

This was an initially investigator-sponsored study; sponsorship was later transferred from GIMEMA (Gruppo Italiano Malattie EMatologiche dell'Adulto) to Incyte.

This was a multicenter, single-arm, open-label study of oral ponatinib in patients with Ph+ ALL ≥ 60 years old or ≥ 18 years old and unfit for intensive chemotherapy and SCT.

3.4.2.2.1. Methods

Study participants

Key eligibility criteria

- Ph+ ALL, and no prior history of CML.
- Patients with previously untreated Ph+ and/or BCR/ABL + ALL:
  - age ≥ 60 years old or
  - age ≥ 18 years old, but unfit for program of intensive therapy and allogeneic SCT.
- Adequate hepatic function as defined by the following criteria:
  - total serum bilirubin ≤1.5 x upper limit of normal (ULN), unless due to Gilbert's syndrome
  - alanine aminotransferase (ALT) ≤2.5 × ULN
  - aspartate aminotransferase (AST) ≤2.5 × ULN.
- Adequate pancreatic function defined as serum lipase and amylase ≤1.5 × ULN.

Key exclusion criteria

- WHO performance status ≤ 50% (Karnofsky) or ≥ 3 (ECOG).
- History of alcohol abuse.
- Uncontrolled hypertriglyceridemia (triglicerides > 450 mg/dL).
- Clinically significant, uncontrolled, or active cardiovascular disease, specifically including, but not restricted to:
  - any history of myocardial infarction, stroke, or revascularization
  - unstable angina or transient ischemic attack within 6 months prior to enrollment
  - congestive heart failure within 6 months prior to enrollment, or left ventricular ejection fraction (LVEF) less than lower limit of normal per local institutional standards within 6 months prior to enrollment
  - history of clinically significant (as determined by the treating physician) atrial arrhythmia
  - any history of ventricular arrhythmia
  - any history of venous thromboembolism including deep venous thrombosis or pulmonary embolism.
- Uncontrolled hypertension (diastolic blood pressure >90 mm Hg; systolic >140 mm Hg). Patients with hypertension should be under treatment on study entry to effect blood pressure control.
- Taking medications that are known to be associated with Torsades de Pointes.
- Creatinine level > 2.5 mg/dl or Glomerular Filtration Rate (GFR) < 20 ml/min

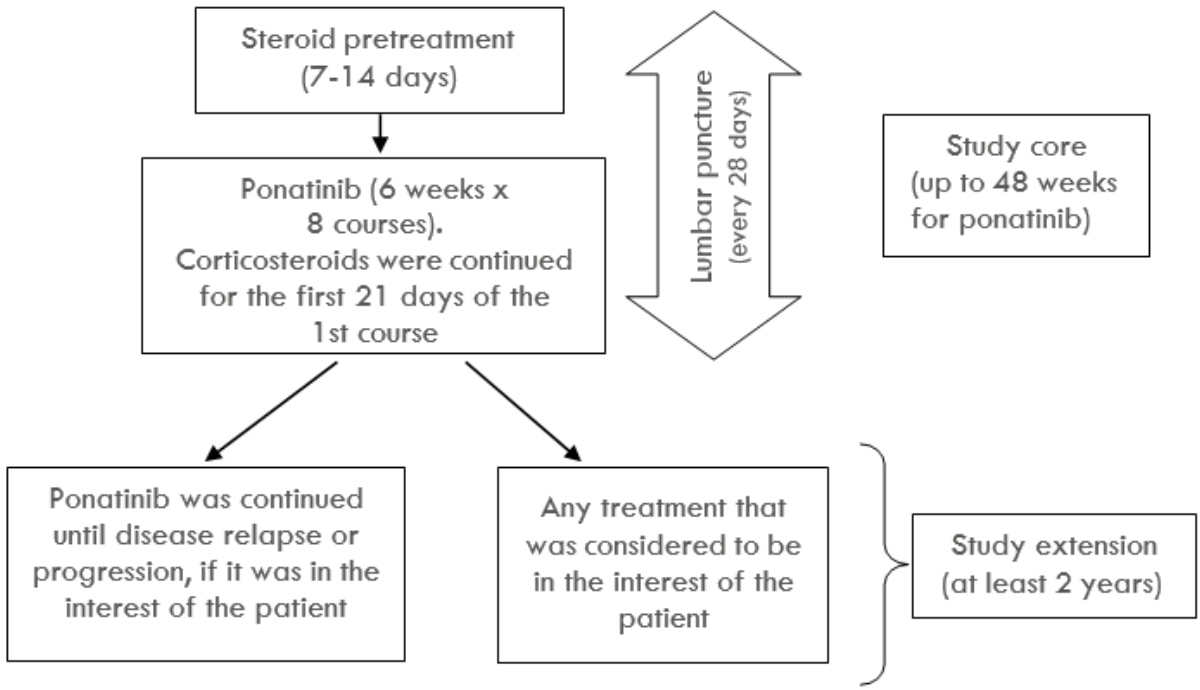
Assessor's comment:

The wording 'unfit for program of intensive therapy and allogeneic SCT' in the inclusion criteria was not fully aligned with the initially sought indication, in which the wording was instead "not eligible to receive chemotherapy-based regimens", that implies a target population consisting of patients that are not at all expected to be chemotherapy candidates. The MAH has amended its claim to those "unfit for intensive chemotherapy and allogeneic stem cell transplant". It remains, however, that the target population of the sought indication may consist of more frail patients than those patents included in the study, exemplified by the fact that 8 of the 44 enrolled patients "unfit for ASCT" did actually receive SCT. The MAH still needs to justify the external validity of the generated data with regard to the relationship between the study population and the proposed target population as described by the therapeutic indication.

Treatments

Figure 4 Overview of study design and treatment in study INCB 84344-201 (fig 1 Study Design)

Figure 1: Study Design



Source CSR section 3.1

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. Participants were to receive daily oral administration of ponatinib at a dose of 45 mg/day for 6 weeks (defined as one course) for 8 courses, with the same dose and schedule, for a total of 48 weeks. Each participant was to be treated for a minimum of 6 weeks, after which they could be discontinued in the following situations:

- Lack of CHR, at the end of the first course (6 weeks);

- Lack of CCgR, at the end of the third course (18 weeks) (this was planned but not measured);
- Loss of CHR or CCgR, at any time.

Prednisone was administered to all participants for 7 to 14 days before ponatinib, to evaluate the response to prednisone alone whilst waiting for the results of cytogenetic and molecular tests. Prednisone was continued for the first 21 days of the first course and then tapered from Day 22 until stopped on Day 29.

Intrathecal therapy with methotrexate/cytarabine/dexamethasone every 28 days was mandatory in participants without clinical cytologic evidence of meningeal involvement. In participants with CNS disease, intrathecal therapy was performed twice weekly until a complete clearance of cerebrospinal fluid blast cells was achieved, once weekly for 4 weeks after that, and once monthly thereafter (for intrathecal therapies administered, refer to INCB 84344-201 CSR Listing 99.14.3).

After 48 weeks, participants could continue the treatment for at least another 2 years (extension phase of the study), if they benefited from the study drug, until disease relapse or progression. Alternatively, participants were allowed to receive any treatment that was in their interests.

Ponatinib dose escalation was not allowed.

Dose reductions of ponatinib (to 30 or 15 mg) were permitted in the event of Grade 3 or Grade 4 AEs; in the event of hematologic AEs, dose reductions were permitted only after CHR was achieved.

Assessor's comment:

Each participant was to be treated for a minimum of 6 weeks, after which "patients (*sic*) could be discontinued" in the following situations (i) Lack of CHR at the end of the first course (6 weeks), or (ii) Lack of CCgR, at the end of the third course (18 weeks) (this was planned but not measured), or (iii) Loss of CHR or CCgR, at any time. The MAH has clarified that the Protocol only specified that participants should be treated for a minimum of 6 weeks and could continue treatment in the above-described situations (i) to (iii); that is, discontinuation would be optional at the discretion of the investigator. Thus, the continuation of treatment with ponatinib in some cases corresponding to these criteria is still in line with the Protocol, according to the MAH. It is noted that treatment discontinuation is an EFS event. This does not seem appropriate, but the prespecification is conservative.

The MAH has also clarified that, since cytogenetic response was not consistently assessed in all participants at all planned timepoints and specifically no assessment was performed at Week 18, none of the participants were discontinued from ponatinib for not having reached CCgR at the subsequent timepoint when this analysis was performed (ie, Week 24). It is noted that CCgR was measured both at week 12 (43% had CCgR) and week 24 (55% had CCgR).

After 48 weeks, participants could continue the treatment for at least another 2 years (extension phase of the study), if they benefited from the study drug, until disease relapse or progression. Alternatively, participants were allowed to receive any treatment that was in their interests. The MAH needs to justify the recommendation in SmPC section 4.2 which states that discontinuing ponatinib should be considered if a complete haematologic response has not occurred by 3 months, since this timeframe was not studied in Study INCB 84344-201.

The MAH has added somewhat excessive information on given CNS prophylaxis or treatment in SmPC section 5.1, which needs to be shortened.

Objectives and endpoints

Primary and secondary objectives and endpoints are described in Figure 5.

Figure 5 Study objectives and endpoints in study INCB 84344-201

Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the therapeutic effects of ponatinib in patients with Ph+ ALL who are 60 or more than 60 years old, or are unfit for chemotherapy and SCT. Since in these patients, the rate of CHR with other TKIs is already close to 100%, but the relapse rate at 1 year is 50% or more, the purpose of this study was to induce better and longer remissions.	The proportion of participants who were in CHR at 6 months, calculated on the total number of participants enrolled who had received at least 1 dose of the first drug (prednisone).
Secondary	
To evaluate: • The CHR at 6, 12, 24, 36, and 48 weeks • The CCgR at 6, 12, 24, 36, and 48 weeks and duration of CCgR • The CMolR and MMolR at 12, 24, 36, and 48 weeks, and the duration of CMolR • Type and number of BCR-ABL kinase domain mutations developing during and after the study[a] • Relationship between the response and the biomarkers[a] • Event-free survival • Overall survival • Failure-free survival[b] • The treatment toxicity	Secondary endpoints were: • The rate of CHR at 6, 12, 24, 36, and 48 weeks • The rate of CCgR at 6, 12, 24, 36, and 48 weeks and duration of CCgR • The rate of CMolR and MMolR at 12, 24, 36, and 48 weeks, and the duration of CMolR • Type and number of BCR-ABL kinase domain mutations developing during and after the study[a] • Relationship between the response and the biomarkers[a] • Event-free survival • Overall survival • Failure-free survival[b] • Side effects, AEs and SAEs

AE = adverse event; CCgR = complete cytogenetic response; CHR = complete hematologic response; CMolR = complete molecular response; MMolR = major molecular response; Ph = Philadelphia; SAE = serious adverse event; SCT = stem cell transplantation.

[a] These objectives and endpoints were planned in the Protocol. However, following the transfer of study sponsorship from GIMEMA to Incyte on 30 JUL 2019, Incyte decided not to continue to explore these parameters because at this time the participants were very advanced in terms of study treatment and follow-up and the data were incomplete, and therefore no conclusions could be drawn.

[b] Failure-free survival was planned but not estimated as the cytogenetic response was not measured at 18 weeks.

Source CSR section 2

Definitions of endpoints

Complete **hematologic** response (CHR) requires that all of the following are present:

- BM with less than 5% blast cells and peripheral blood differential without blasts
- Polymorphonuclear leukocytes ≥ 1.5 × 109/L and platelets ≥ 100 × 109/L

- No evidence of extramedullary involvement from leukemia

Cytogenetic response (the percentage of Ph+ metaphases, as evaluated by chromosome banding analysis of at least 20 marrow cell metaphases)

- Complete cytogenetic response (CCgR): Ph+ = 0%.
- Partial cytogenetic response (PCgR): Ph+ = 1% to 34%.
- Minor cytogenetic response (mCgR): Ph+ = 35% to 65%.
- Minimal or none cytogenetic response (min/none CgR): Ph+ > 65%.

Molecular response (the ratio between BCR-ABL and ABL, assessed using RT-qPCR)

- Complete molecular response (CMolR) if by RT-qPCR the BCR-ABL: ABL ratio was < 0.01, with a sensitivity of at least 30,000 molecules of ABL.
- Major molecular response (MMolR) if by RT-qPCR the BCR-ABL: ABL ratio < 0.10, with a sensitivity of at least 30,000 molecules of ABL.

EFS was defined as the length of time from the date of enrollment (date of steroid first dose) to the date of the event. Event was defined as follows: failure to achieve CHR at Week 6, treatment discontinuation, CHR lost, or death by any cause.

OS was defined as the interval between the date of enrollment (date of steroid first dose) and the date of death due to any cause.

Translational research endpoints (BCR-ABL kinase domain mutations developing during and after the study, and relationship between the response and the biomarkers) were planned but not performed in more than 3 patients following the transfer of study sponsorship from GIMEMA to Incyte.

Assessor's comment:

CHR at 6 months as the primary endpoint, can be accepted in principle, since the study design and CHR endpoint allow for the isolation of an effect of ponatinib, despite the single-arm design of the study (steroids alone would be anticipated to contribute negligibly to efficacy at 6 months).

The pre-defined secondary endpoints including duration of EFS, and OS are time dependent endpoints that are considered unsuitable to isolate drug effects in a single-arm trial. Thus, this data needs to be interpreted with caution in this setting. The MAH is asked to remove EFS and OS data from SmPC section 5.1.

Unlike the pre-defined endpoints in the protocol, duration of CHR was not included as an objective or endpoint in the protocol. Rather, it was planned as an efficacy endpoint in the SAP that was written more than three years after last participant enrolled. Endpoints introduced late during a study raise concerns regarding changes being data driven. In this case, it could be agreed that duration of CHR is in alignment with the primary objective (further, see below under Sample size). Currently, a Kaplan-Meier plot of duration of CHR is presented in the SmPC section 5.1.

Further, it is noted that both in the SAP and in the CSR, the MAH states that the secondary endpoint failure-free survival was planned but not estimated as the cytogenetic response was not measured at week 18. However, according to the protocol section 9.3, failure-free survival is measured in all patients from the date of enrollment, and failure is defined as (i) failure of achieving CHR or loss of CHR, or (ii) death by any causes. Thus, according to the protocol, cytogenetic response is not needed to estimate failure-free survival, as implied in the SAP and in the CSR.

Sample size

The hypothesis tested was that 75% of participants using ponatinib would be in CHR at 6 months, as compared to 55% of participants shown to be in CHR at 6 months with imatinib (Vignetti et al 2007). The sample size needed to test the hypothesis with α = 0.05 and 80% power was 37 as estimated using the "Sample size tables for exact single-stage phase II design" (A'hern 2001). The total number of participants was adjusted to 44 to account for 20% dropouts and protocol violations.

Assessor's comment:

The study hypothesis underlying the sample size calculation, was that 75% of subjects using ponatinib would be in CHR at 6 months (primary endpoint). The null hypothesis, to be rejected in favour of the alternative, was based on a reference with CHR rate of 55% at 6 months with imatinib treatment (Vignetti et al 2007), as reported by the MAH. However, the study primary objective stated that; "Since in these patients, the rate of CHR with other TKI is already closed to 100%, but the relapse rate *at 1 year is 50% or more*, the purpose of this study is to induce better and longer remissions". The misalignment of the primary endpoint and primary objective serves to highlight the exploratory nature of this study. In addition, it is noted that the background reference for the primary endpoint (i.e. 55% of participants treated with imatinib in CHR at 6 months) cannot be found within the text in the Brief report from Vignetti et al 2007, but rather assumed from the associated disease-free survival (DFS) curve, which actually shows DFS 65% at 6 months, provided that events on the Kaplan Meier DFS curve is constituted by loss of CHR.

The sample size estimation can be followed given the assumptions made for the primary endpoint. The sample size is nevertheless very limited and poses an uncertainty in terms of interpretation of results beyond the primary endpoint. The small sample size contributes to concerns relating to generalizability of the reported results, in turn related to the potential selection of patients given the study design. It is not clear that external validity can be ascertained based on such a small sample size.

Randomisation and Blinding (masking)

This was a single-arm open-label study.

Statistical methods

According to the original SAP dated 12 March 2020 (based on Protocol Amendment 3 dated 15 October 2019), this is an open-label, single-arm study. Hence, p-values will not be provided, and multiple adjustment will not be made. No updated versions of SAP are submitted.

Analysis population

The full analysis set (FAS) included all participants enrolled in the study who received at least 1 dose of study drug. The FAS was used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy and safety data. All 44 participants (100.0%) were included in the FAS.

Analysis of efficacy parameters

Efficacy parameters were summarized using descriptive statistics. For categorical measurements, summary statistics included sample size, frequency, and percentages. For continuous measurements, summary statistics included sample size, mean, median, STD, standard error of the mean, minimum, and maximum. Summary statistics for continuous measures were provided for baseline, the actual

measurements at each visit, and the change and percentage change from baseline at each visit, if applicable.

Time-to-event endpoints, including duration of CHR, duration of CCyR, duration of CMR, EFS, and OS, were analysed using the KM method. Median survival time was estimated using the KM method. Confidence intervals for median survival time were calculated using the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982).

No interim statistical analysis was performed.

Assessor's comment:

The original SAP is dated 12 March 2020, which is more than three years after last participant enrolled. The MAH states that the original SAP is based on protocol amendment 3 dated 15 October 2019. However, protocol amendment 2 dated 30 July 2019 is the most recent protocol version submitted within this application. Upon request to supplement the application with the protocol version amendment 3, the MAH clarified the original version of the SAP was based on Protocol Amendment (Version) 2 (30 JUL 2019). The SAP reference to Protocol Amendment (Version) 3 dated 15 OCT 2019 is admitted having been a mistake. Protocol version 3 was prepared although was never implemented.

Before sponsorship change to Incyte, three "Treatment Advisory Committee" representatives (from Bologna site and GIMEMA) reviewed the complete safety and efficacy data of 27 participants that had started the extension phase upon the data information at the time the change of the sponsorship 30 JUL 2019. No formal documentation on the Treatment advisory committee meetings were made available by GIMEMA at time of the sponsorship change. The MAH was asked to clarify if Incyte had any insight in the available study results when for example the original SAP was written, and describe which data driven elements that were implemented in the SAP. In response, the MAH claims that the SAP reflects the analyses planned by GIMEMA and that the SAP was not informed by any data-driven elements. The MAH further stated that they only received access to the clinical database after completion of the change in sponsorship on 30 JUL 2019. When the database was transferred, no additional data analysis was conducted between the ASH Annual Meeting in 2017 and the analysis that was conducted for the CSR in AUG 2021.

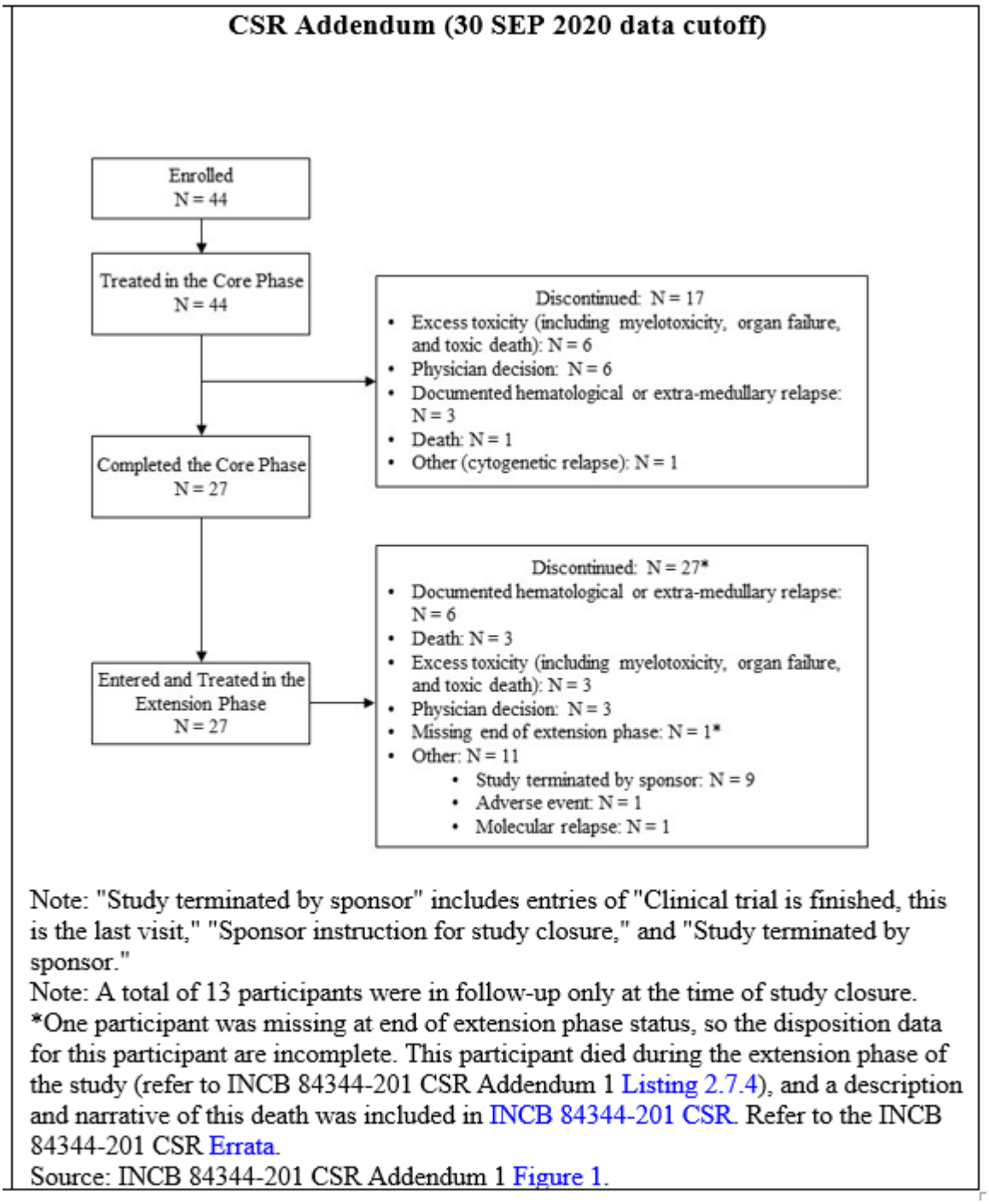
Overall, the analysis as outlined in the SAP is acceptable. However, the open label nature of the study without an adequate control in a small number of patients is a major limitation. As in any open-label study, it will not have been possible to ensure that subjective assessments and decisions were not affected by knowledge of treatment.

Efficacy parameters were summarized using descriptive statistics and no p-values have been provided. This is agreed in this exploratory open-label, single-arm study for which confidence intervals are considered more useful.

3.4.2.2.2. Results

Participant flow

Figure 6 Participant Disposition as per Correction in CSR Addendum 1



Recruitment

Study period:

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.

Until 30 JUL 2019, the study was under GIMEMA sponsorship, after which Incyte became the study sponsor.

Nine participants were considered to receive benefit from ponatinib treatment at the time of sponsor decision for study closure 30 SEP 2021. Each of these participants was transitioned to commercial ponatinib at the end of treatment. At study closure, 13 participants were in follow-up.

In the primary CSR, data is presented from the date the first participant enrolled to a data cut-off date of 24 APR 2020. In the CSR Addendum (30 SEP 2021 data cut-off date), the data collected at baseline include assessments completed on Day 1 that were missing from the primary analysis (24 APR 2020 data cu-toff date) and are aligned with the definitions in the SAP and consistent with the primary CSR, as reported by the MAH.

Study center:

The study was conducted at 23 study centers in Italy. A total of 44 participants were enrolled at 22 study centers. One additional study center was initiated; this center had 1 screen failure and did not enrol any participants.

Assessor's comment:

The study enrolled participants from 04 DEC 2014 to 24 JAN 2017. Two and a half year after finished enrollment, Incyte became the sponsor from 30 JUL 2019.

According to the protocol, the study duration (enrolment + therapy duration + follow-up) was approximately 5 years. Sponsor decision for study closure was made 30 SEP 2021.

Conduct of the study

The original Protocol's name and date, as well as protocol amendments are summarized in Table 14.

All participants were enrolled under the Protocol Amendment #1 dated 07 JUL 2014.

Table 14 Amendments to the GIMEMA Protocol dated 02 JUL 2012

GIMEMA Protocol dated 02 JUL 2012: Front-line treatment of Philadelphia positive (Ph+)/BCR-ABL positive Acute Lymphoblastic Leukemia (ALL) with AP24534 (Ponatinib), 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.	
Protocol Amendment #1 (implemented by GIMEMA) dated 07 JUL 2014	
Purpose	To make administrative updates, to revise the inclusion/exclusion criteria, the study criteria (discontinuation, dose reduction, duration, etc) and assessments, AE definitions and reporting.

Description of changes	• Addition of clinical trial number • Changes in the study administrative structure and writing committee • Updates in study background • Revision of inclusion and exclusion criteria • Revision of treatments/concomitant therapies: addition of aspirin and/or a statin treatment, once a CHR was achieved, as clinically indicated • Revision of study duration: changed to 5 years • Revision of the assessment of risks and benefits • Revision of discontinuation criteria and of conditions for ponatinib dose reductions • Revision of assessments and tests to be carried out during and after the study core and extension phase, and at withdrawal and/or treatment failure • Revision of definitions of AEs and their causality assessment • Revision of SAE and SUSAR reporting • Addition of appendices "Thromboembolism Risk Factor Assessment Scale" (Appendix C) and "Expected AEs from GIMEMA sponsored studies" (Appendix H)
Rationale for changes	To implement changes in study methods/criteria and administrative changes
Amended sections	**All sections were affected.**
Other changes	• Address of TAC was modified • Paragraph in Section 22.3 Central Review Procedures was updated • References were updated • Appendix I "World Medical Association Declaration of Helsinki" was updated

Source CSR section 6.1

Table 14. Amendments to the GIMEMA Protocol dated 02 JUL 2012 (Continued)

Protocol Amendment #2 (Incyte) dated 30 JUL 2019	
Purpose	To modify the name of the study sponsor from GIMEMA to Incyte and update the study contacts.
Description of changes	The page presentation, sponsor name and address, study contacts, and study amendment reference number were updated.
Rationale for changes	To align with change in the sponsor's name.
Amended sections	1. Title page; Investigator's Agreement; Synopsis; Section 2.5.3, Imatinib and dasatinib as single-agent in de novo elderly and young Ph+ ALL; Section 6.1, Drug information; Section 7, Drug supply; Section 10.1, Sample collection and storage; Section 11.1, Sample size; Section 11.4, Analysis; Section 17, Investigator authorization procedure; Section 19, Forms and procedures for collecting data; Section 20.2.2, Serious adverse events or suspected unexpected serious adverse reactions; Section 21,Treatment Advisory Committee (TAC); Section 22.2, On-site quality control; Section 22.3, Central review procedures; Section 23.3, Informed consent; Section 24, Administrative responsibilities; Section 25, Trial sponsorship and financing; Section 26, Trial insurance; Section 27, Publication policy; Appendix G, Timepoints and procedures for collecting and mailing of biological samples.
Other changes	Incorporation of administrative changes. Other minor, administrative changes were incorporated throughout the Protocol.

Source CSR section 6.1

Changes in Conduct of the Study except those included in Protocol amendments

- It was planned in the protocol that treatment compliance would be assessed. However, drug compliance and drug accountability data were not collected during the GIMEMA sponsorship and were implemented when Incyte became the sponsor.
- During the study core phase, it was planned that participants could be discontinued at the end of the third course because of lack of CCgR. However, CCgR was not scheduled to be assessed at this timepoint.
- Prior and concomitant medications and post-therapy medications were not captured in the GIMEMA eCRF but were requested to be recorded in the Incyte eCRF, and at the date of cutoff the data were not fully complete.
- Biochemistry parameters were not captured in the GIMEMA eCRF with absolute values but with ranges, not fully aligned with NCI CTCAE v4.0. The Incyte eCRF collected absolute values.

Conduct Changes Before Sponsorship Change

- Translational research (one of the secondary endpoints) was not performed. Data was not available to evaluate the relationship between the response and the biomarkers. Further, regarding the type and number of BCR-ABL kinase domain mutations developing during and after the study, Incyte decided not to continue exploring these parameters since it was considered that no conclusion could be drawn based on partial data/information.
- Based upon the data information at the time the sponsorship was transferred from GIMEMA to Incyte on 30 JUL 2019, 17 participants had discontinued the study core phase and 27 participants had entered and therefore started the extension phase. Per Protocol requirements

(refer to Section 21 of the Protocol), the complete data and information concerning safety and efficacy (continuation beyond the core phase) of these 27 participants was required to be reviewed by 3 treatment Advisory Committee (TAC) representatives (from Bologna site and GIMEMA). No formal documentation on the TAC meetings were made available by GIMEMA at time of the sponsorship change.

Changes in Statistical Methods and Planned Analyses Prior to Database Lock

- The duration of CHR was not included as an objective and endpoint in the Protocol but was planned as an efficacy endpoint in the SAP, which was completed as a large part of results were available (original statistical analysis is dated 12 March 2020)
- FFS was not estimated because the CCgR was not assessed at Week 18.
- Study drug compliance was not summarized since neither drug compliance nor drug accountability data were collected. A dose modification table was presented instead.
- Descriptive statistics were to be provided for the duration of steroid pre-treatment, according to the SAP. However, a summary of steroid pre-treatment was not presented because the data were incomplete.

Protocol Deviations

Protocol deviations were not collected in the database in the eCRF; the Incyte eCRF only captured reported eligibility criteria deviations. In the eCRF, a total of 2 participants were included in the study even though they did not meet inclusion criterion number 4 "adequate pancreatic function as defined by serum lipase and amylase ≤ 1.5 x ULN".

Six patients had confirmed ponatinib dose re-escalations after a dose decrease, which was not allowed during the study. These deviations were not reported in the general deviation's tracker.

Global Protocol deviations were to be reported for the TAC for which no formal documentation was made available to Incyte at time of sponsorship change.

The overall Protocol deviations were captured separately by Incyte's representative.

No Protocol deviations significantly affected the completeness, accuracy, and/or reliability of the study data or affected the study conclusions as reported by the MAH.

Assessor's comment:

The original protocol was dated protocol 02 JUL 2012. After two years (07 JUL 2014), changes were made according to Protocol Amendment #1. Enrollment started first after this amendment, and, all participants were enrolled under the Protocol Amendment #1 dated 07 JUL 2014.

The MAH reports that a number of changes in the conduct of the study took place in addition to the protocol amendments. For example, treatment compliance was planned in the protocol, but drug compliance and drug accountability data were not collected during the GIMEMA sponsorship and were implemented first when Incyte became the sponsor two and a half year after finished enrollment. This issue is considered to reinforce the uncertainty of the external validity study results.

Prior and concomitant medications and post-therapy medications were not captured in the GIMEMA eCRF but were requested to be recorded in the Incyte eCRF, and at the date of cutoff the data were not fully complete.

The MAH reports that no protocol deviations significantly affected the completeness, accuracy, and/or reliability of the study data or affected the study conclusions. However, protocol deviations were not collected in the database in the eCRF; the Incyte eCRF only captured reported eligibility criteria deviations. In the eCRF, a total of 2 participants were included in the study even though they did not meet inclusion criterion on adequate pancreatic function. Further, six patients had confirmed ponatinib dose re-escalations after a dose decrease, which was not allowed during the study. These deviations were not reported in the general deviation tracker. Global Protocol deviations were to be reported for the Treatment advisory committee for which no formal documentation was made available to Incyte at time of sponsorship change. The MAH states that the overall protocol deviations were captured separately by Incyte's representative. The management of protocol deviations is considered to bring additional uncertainty to the generated data.

Baseline data

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

All participants in this study were previously untreated for Ph+ ALL. Prednisone was administered to all participants for 7 to 14 days before ponatinib.

Table 15 Summary of Baseline Disease Characteristics (Full Analysis Set)

	Total (N = 44)
Time since initial diagnosis of ALL, days	
N	44
Mean (STD)	15.4 (9.72)
Median (min, max)	13.5 (5, 66)
WHO performance status (ECOG), n (%)	
0	23 (52.3)
1	17 (38.6)
2	3 (6.8)

Missing	1 (2.3)
BM cellularity, n (%)	
Hyper	26 (59.1)
Normal	7 (15.9)
Hypo	8 (18.2)
Missing	3 (6.8)
BM lymphocytes/leukocytes, %	
N	36
Mean (STD)	14.5 (19.10)
Median (min, max)	10.0 (0, 80)
BM blasts/leukocytes, %	
N	41
Mean (STD)	75.0 (20.55)
Median (min, max)	80.0 (0, 98)
CNS, n (%)	
No	36 (81.8)
Yes	6 (13.6)
Missing	2 (4.5)
BCR-ABL transcript level in BM, n (%)	
p190	29 (65.9)
p190/210	4 (9.1)
p210	7 (15.9)
Missing	4 (9.1)

ALL = acute lymphoblastic leukemia; BCR-ABL = breakpoint cluster region-Abelson; BM = bone marrow; CNS = central nervous system; CSR = Clinical Study Report; ECOG = Eastern Cooperative Oncology Group; max = maximum; min = minimum; STD = standard deviation; WHO = World Health Organization.
Note: Data cutoff date of 30 SEP 2021.
Source: INCB 84344-201 CSR Addendum 1 Table 1.3.

During the study, 75.0% of participants had at least 1 dose reduction. See below for a summary of ponatinib dose modification.

Table 16 Summary of Ponatinib Dose Modification (Full Analysis Set)

Variable	**Total (N = 44)**
Participants with any dose interruption, n (%)	24 (54.5)
Participants with any dose reduction, n (%)	33 (75.0)
Participants with any dose interruption and any dose reduction, n (%)	23 (52.3)
Participants with any dose modification due to:	

Hematological toxicity, n (%)	5 (11.4)
Medical decision, n (%)	19 (43.2)
Nonhematological toxicity, n (%)	25 (56.8)
Other, n (%)	3 (6.8)

Note: Participants with multiple dose modifications were counted once under each reason.
Source CSR section 7.8.2

Post-therapy was reported for 14 participants (31.8%). Post-therapy medications reported in > 5% of participants by medication class were:

- Protein kinase inhibitors reported for 7 participants (15.9%)
- Other therapeutic products reported for 6 participants (13.6%); these 6 participants all underwent SCT
- Monoclonal antibodies reported for 4 participants (9.1%).

Assessor's comment:

The amended indication wording is 'unfit for intensive chemotherapy and allogeneic stem cell transplant'. It is noted that eight participants (18%) did actually receive SCT as post-ponatinib therapy (according to ad-hoc analysis in CSR Addendum), despite the inclusion criteria 'unfit for program of intensive therapy and allogeneic SCT'. The MAH still needs to justify the external validity of the generated data with regard to the relationship between the study population, which is only n=44, all from the same country, and the proposed target population.

Numbers analysed

The FAS included all participants enrolled (n=44) in the study who received at least 1 dose of study drug. The FAS was used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy and safety data.

Outcomes and estimation

Efficacy results – **Primary CSR**

At the time of the primary CSR data cut-off date (24 APR 2020), 10 participants remained on the extension phase of the study and were still receiving study treatment with ponatinib, and 14 additional participants remained in study follow-up.

Primary endpoint – **Primary CSR**

The primary endpoint was the proportion of participants who were in CHR at 6 months. See Table 17.

Table 17 Complete Hematologic Response at 6 Months (Full Analysis Set)

	Total (N = 44)
Participants achieving CHR at Week 24[a], n (%)	
Yes	38 (86.4)
No/missing[b]	6 (13.6)

CHR = complete hematologic response
Note: Participants with missing postbaseline values were imputed as nonresponders. Participants who discontinued prior to that visit were included in missing category.
Note: Data cutoff date of 24 APR 2020.
[a] Response at Week 24 includes 1 participant who was assessed at Week 20.
[b] Of the 6 participants who did not achieve CHR, 1 had a fatal AE (refer to INCB 84344-201 CSR Listing 2.7.4), 2 had fatal TEAEs (refer to INCB 84344-201 CSR Section 10.2.1), 1 relapsed at Week 12, and data were not available or missing at Week 24 for 2 participants (refer to INCB 84344-201 CSR Listing 2.6.1.1).
Source: INCB 84344-201 CSR Table 2.1.1

Secondary endpoints - **Primary CSR**

Overall responses by time

A summary of responses for the secondary efficacy endpoints at Weeks 6, 12, 24, 36, and 48 is provided in Table 18.

Table 18 Study INCB 84344-201 Summary of Responses (Full Analysis Set)

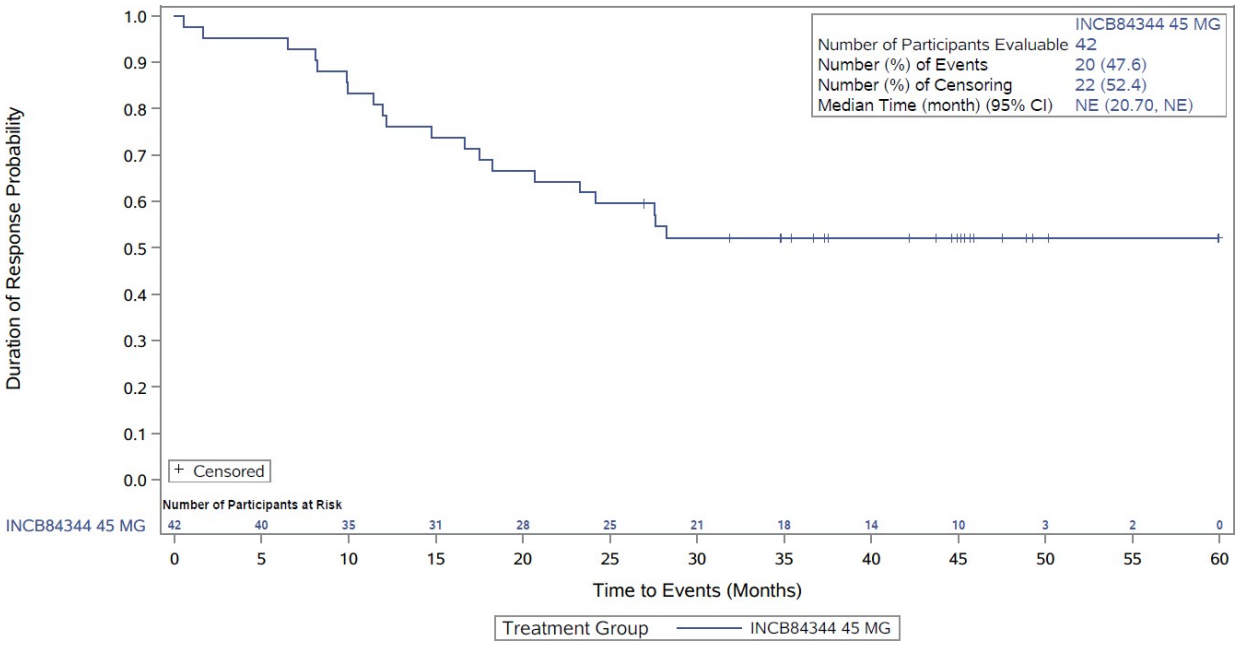
N = 44	Week 6	Week 12	Week 24[a]	Week 36	Week 48
CHR, n (%)	40 (90.9)	37 (84.1)	38 (86.4)	29 (65.9)	25 (56.8)
CCyR, n (%)	21 (47.7)	19 (43.2)	24 (54.5)	16 (36.4)	15 (34.1)
CMR, n (%)	21 (47.7)	21 (47.7)	18 (40.9)	18 (40.9)	16 (36.4)
MMR, n (%)	15 (34.1)	11 (25.0)	14 (31.8)	8 (18.2)	6 (13.6)

CCyR = complete cytogenetic response; CHR = complete hematologic response; CMR = complete molecular response; MMR = major molecular response.
Note: Participants with missing postbaseline values were imputed as nonresponders. Participants who discontinued prior to that visit were included in missing category.
Note: Data cutoff date of 24 APR 2020.
[a]Response at Week 24 includes 1 participant who was assessed at
week Source: INCB 84344-201 CSR Tables 2.1.1, 2.2.1, and 2.3.1.

Duration of CHR

With a median follow-up of 44.9 months at the data cut-off date (data on file), the median duration of CHR had not been reached at the data cut-off (24 APR 2020), see Figure 7.

Figure 7 Study INCB 84344-201 Kaplan-Meier Estimates of Duration of CHR (Full Analysis Set)



CI = confidence interval; NE = not evaluable.

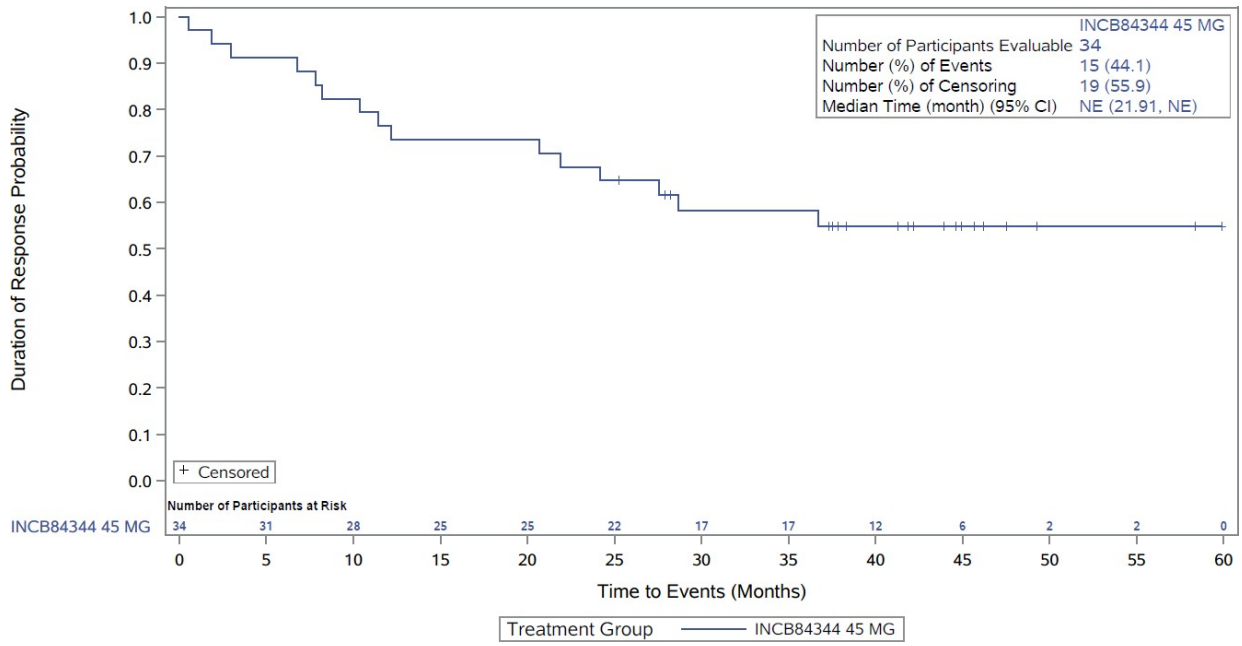
Note: Data cutoff date of 24 APR 2020.

Source: INCB 84344-201 CSR Figure 2.4.

Duration of CCyR

The median duration of CCyR was not reached due to the number of participants remaining in CCyR at the last assessment or at the time of data cut-off (24 APR 2020), see Figure 8.

Figure 8 Study INCB 84344-201 Kaplan-Meier Estimates of Duration of CCyR (Full Analysis Set)



CI = confidence interval; NE = not evaluable.

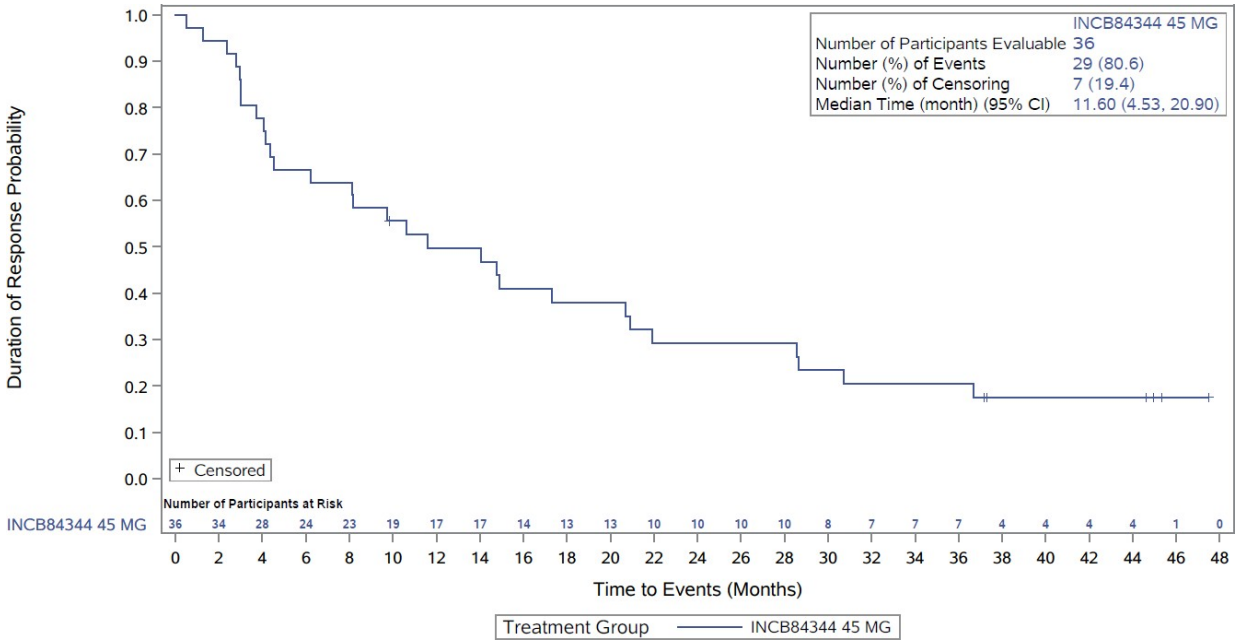
Note: Data cut-off date of 24 APR 2020.

Source: INCB 84344-201 CSR Figure 2.5.

Duration of CMR

The median duration of CMR was estimated as 11.60 months (95% CI: 4.53, 20.90), see Figure 9.

Figure 9 Study INCB 84344-201 Kaplan-Meier Estimates of Duration of CMR (Full Analysis Set)



CI = confidence interval

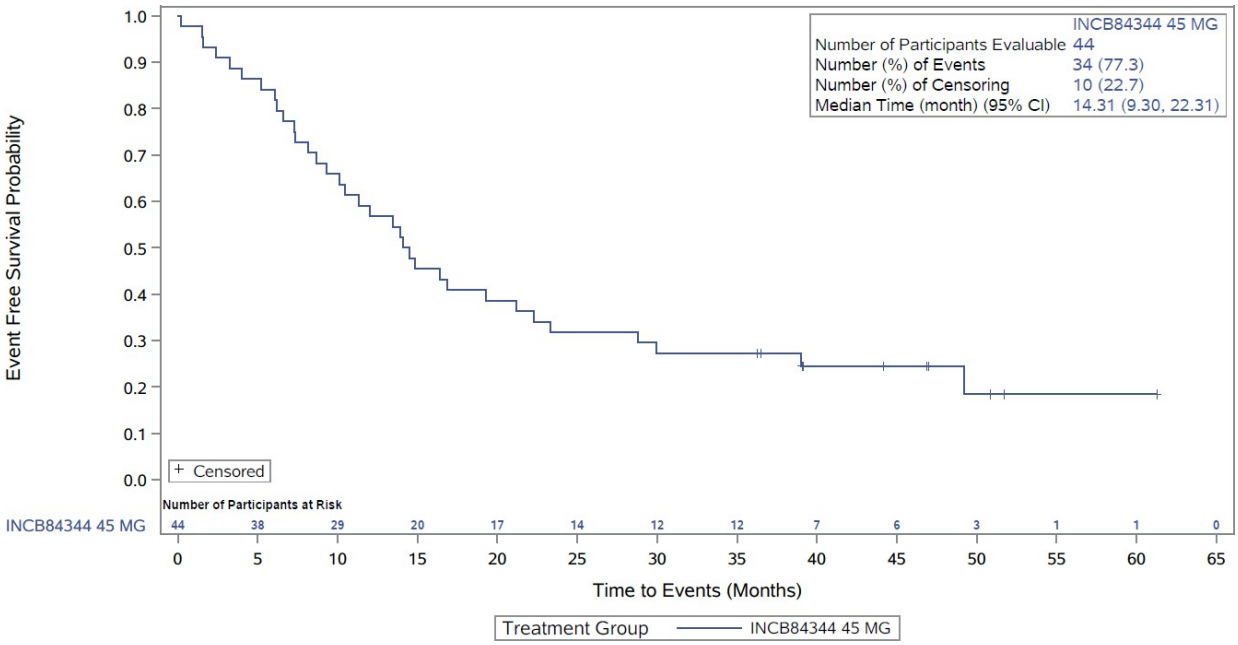
Note: Data cut-off date of 24 APR 2020.

Source: INCB 84344-201 CSR Figure 2.6.

Event-free survival

With a median follow-up of 46.9 months (data on file), the median EFS was estimated 14.31 months (95% CI: 9.30, 22.31), see Figure 10.

Figure 10 Study INCB 84344-201 Kaplan-Meier Estimates of EFS (Full Analysis Set)



CI = confidence interval;
Note: Data cut-off date of 24 APR 2020.

Source: INCB 84344-201 CSR Figure 2.7.

Overall survival

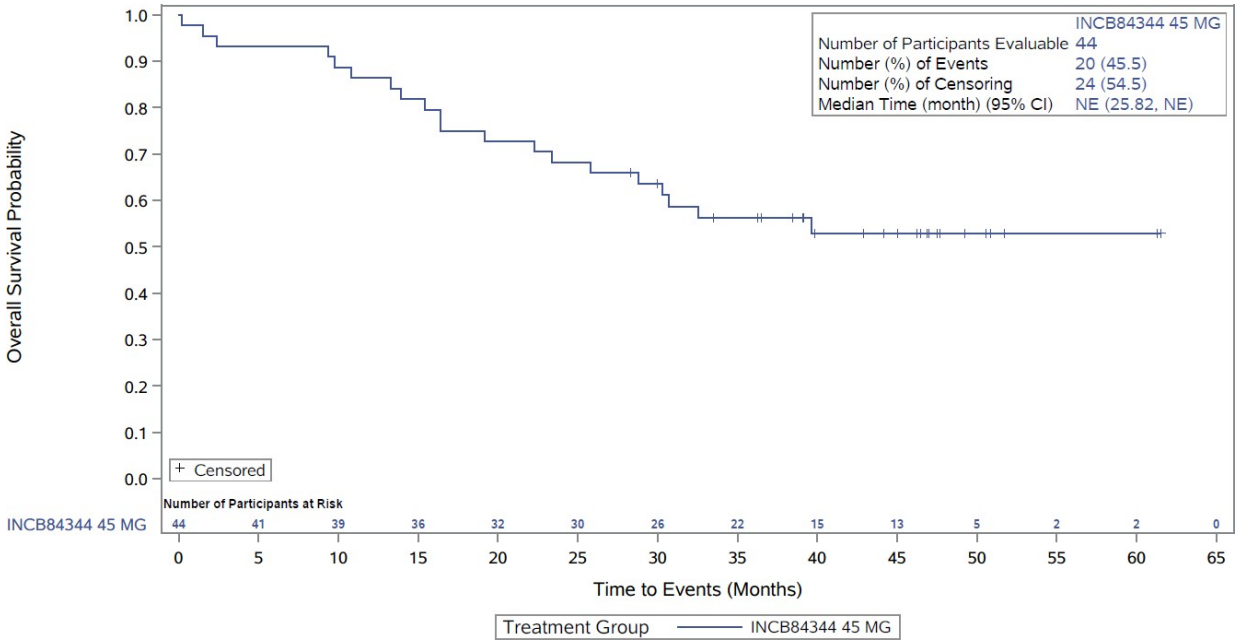
The median OS was not reached at the last assessment or at the time of data cut-off (24 APR 2020), see Table 19 and Figure 11.

Table 19 Study INCB 84344-201 Overall Survival (Full Analysis Set)

	Total (N = 44)
Participants who died, n (%)	20 (45.5)
Participants censored, n (%)	24 (54.5)
Median time to death, months (95% CI)[a]	NE (25.82, NE)

[a]The 95% CI was calculated using the method of Brookmeyer and Crowley (Brookmeyer and Crowley 1982). CI = confidence interval; NE = not evaluable.
Note: Data cut-off date of 24 APR
2020. Source: INCB 84344-201 CSR
Table 2.5.

Figure 11 Study INCB 84344-201 Kaplan-Meier Estimates of Overall Survival (Full Analysis Set)



CI = confidence interval; NE = not evaluable.
Note: Data cut-off date of 24 APR 2020.
Source: INCB 84344-201 CSR Figure 2.8.

Efficacy results – **CSR Addendum**

Additional data up to study completion, with a final cut-off date of 30 SEP 2021 (refer to INCB 84344-201 CSR Addendum) was added to update longer-term efficacy results.

Results for the Primary Endpoint and for selected Secondary Endpoints with data cut-off date of 30 SEP 2021, are shown in Table 20.

Table 20 Results for the Primary Endpoint and for selected Secondary Endpoints of Study INCB 84344-201 (Data Cut-off Date of 30 SEP 2021)

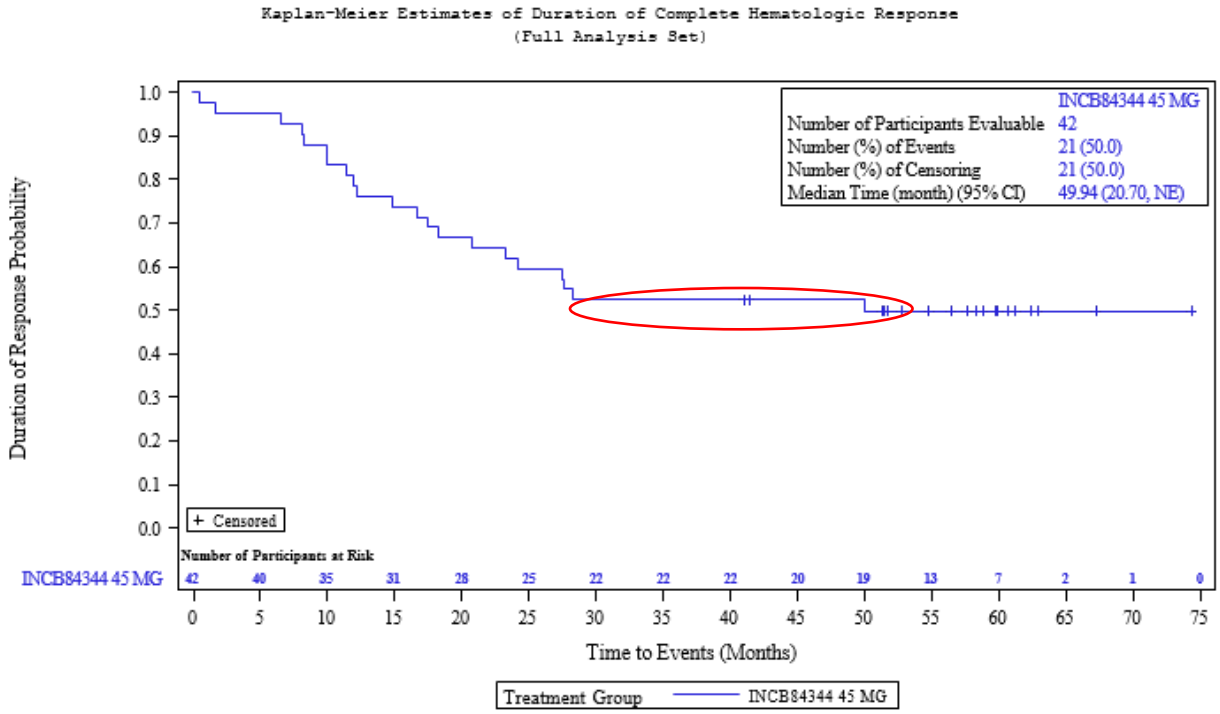
Variable	Total (N = 44)
Primary Analysis of the Primary Endpoint[a]	
Participants achieving CHR at Week 24[b], n (%)	38 (86.4)
Secondary Endpoints: Median Duration of Response	
Median duration of CHR, months (95% CI)	49.94 (20.70, NE)
Median duration of CCyR, months (95% CI)	36.70 (21.91, NE)
Median duration of CMR, months (95% CI)	14.06 (6.24, 21.91)
Median EFS, months (95% CI)	29.54 (18.27, 60.32)
Median OS, months (95% CI)	61.67 (25.82, NE)

CCyR = complete cytogenetic response; CHR = complete hematologic response; CI = confidence interval; CMR = complete molecular response; EFS = event-free survival; MMR = major molecular response; NE = not evaluable; OS = overall survival.
Note: Data cut-off date of 30 SEP 2021.
a This endpoint is reported as of the data cutoff date of 30 SEP 2021, and the result is the same as that which was reported from the data cutoff date of 24 APR 2020.
b Response at Week 24 includes 1 participant who was assessed at Week 20.

Source Summary of Clinical Efficacy section 2.2.7.3

Kaplan-Meier estimates of Duration of CHR is presented in Figure 12. According to the SAP, duration of CHR is measured by the date of the achievement of CHR to the date of CHR loss.

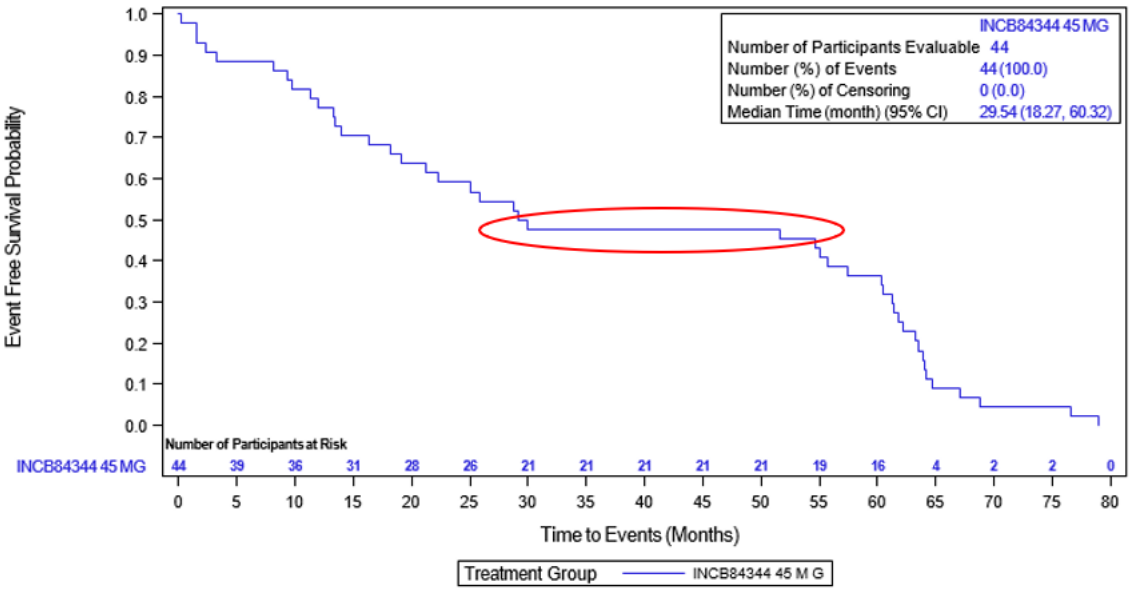
Figure 12 Kaplan-Meier estimates of Duration of CHR (Full Analysis Set)



Source CSR Addendum Figure 2.4

Event-free survival estimated by the Kaplan-Meier method is presented in Figure 13. According to the CSR, event was defined as failure to achieve CHR at Week 6, treatment discontinuation, loss of CHR, or death from any cause.

Figure 13 Event-free survival estimated by the Kaplan Meier method



Source CSR Addendum section 9.2.4

Efficacy results **- Ad-Hoc Analyses**

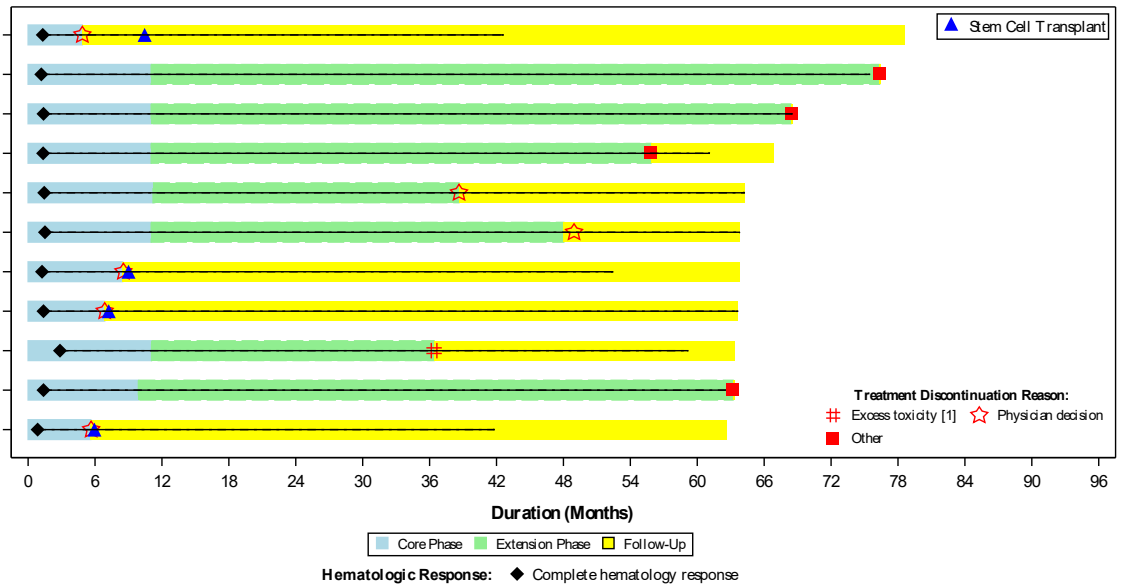
Ad-hoc analyses for participants with BCR-ABL1 KD mutations, participants who received SCT post-study therapy, and participants who had CNS disease at baseline were conducted.

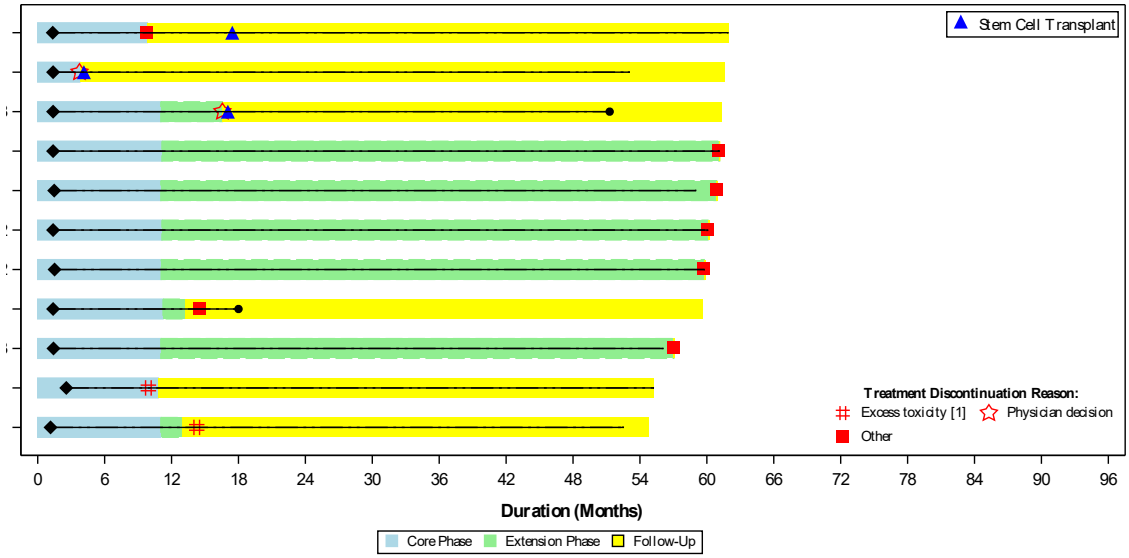
- Evidence for BCL-ABL1 mutations was found in 3 participants (based on a limited number of samples); of the 3 participants with confirmed BCR-ABL1 mutations, 2 relapsed and died during the study (data cut-off date of 30 SEP 2021).
- Eight participants received SCT as post-study therapy after the first remission; 6 were alive at data cut-off, 2 participants died from relapse and disease progression (data cut-off date of 30 SEP 2021).
- Among 6 participants with CNS disease involvement at baseline, all were reported in CHR at Week 6, and none of the participants experienced a documented hematologic relapse. Duration of CHR ranged from 17.51 to 59.83 months, and OS ranged from 19.15 to 67.09 months. Four participants were alive at the data cut-off date of 30 SEP 2021.

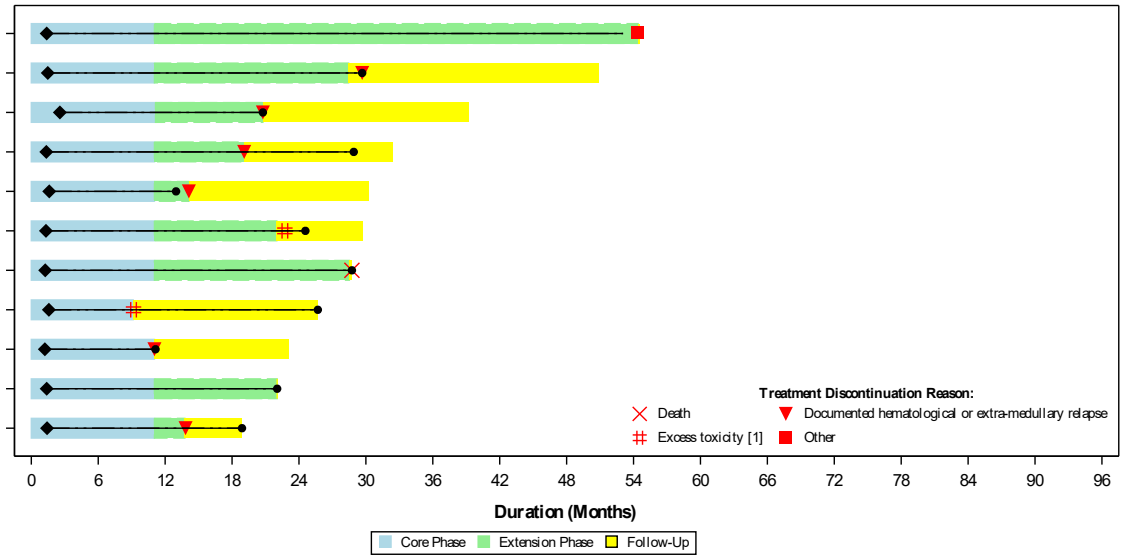
Efficacy results – **Swimmer plot**

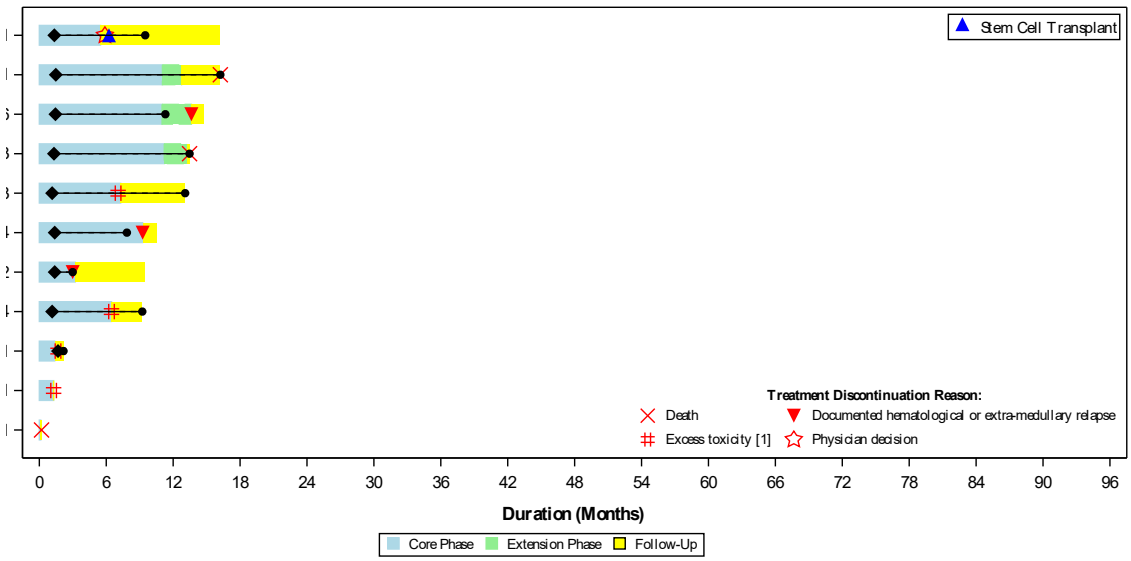
A swimmer plot presents the duration of ponatinib treatment in Study INCB 84344-201, including the reason for discontinuation, the duration of hematologic response, the occurrence of HSCT, and study follow-up for each participant.

Figure 14 Swimmer Plot of Duration of Complete Hematologic Response and Duration of Ponatinib Treatment and Follow-Up Periods (Full Analysis Set)




Stem Cell Transplant
Treatment Discontinuation Reason:
Excess toxicity [1]
Physician decision
Other
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96
Duration (Months)
Core Phase
Extension Phase
Follow-Up
Hematologic Response:
Complete hematology response
Lost complete response or death


Treatment Discontinuation Reason:
Death
Documented hematological or extra-medullary relapse
Excess toxicity [1]
Other
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96
Duration (Months)
Core Phase
Extension Phase
Follow-Up
Hematologic Response:
Complete hematology response
Lost complete response or death


Stem Cell Transplant
Treatment Discontinuation Reason:
Death
Documented hematological or extra-medullary relapse
Excess toxicity [1]
Physician decision
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96
Duration (Months)
Core Phase
Extension Phase
Follow-Up
Hematologic Response:
Complete hematology response
Lost complete response or death

Source: INCB 84344-201 Ad Hoc Figure 90.1.

Assessor's comment:

Primary endpoint

According to the protocol, the hypothesis tested was that 75% of participants using ponatinib would be in CHR at 6 months, as compared to 55% of participants shown to be in CHR at 6 months with imatinib (Vignetti et al 2007). Based on the initial data cut-off date of 24 APR 2020, 38 of the 44 participants (86.4%) were in CHR at 6 months. It is noted that 40,9% of the participants were in CMR at the same timepoint, and 54.5% were in CCgR. It is also noted that the proportion of participants in CHR at week 48 was 56%, which does not obviously fulfill the primary objective presented in the protocol, i.e., to induce better and longer remissions than a relapse rate of 50% at 1 year.

The proportion of patients in CHR at 6 months (86%), isolates a drug effect of ponatinib in the studied population with newly diagnosed Ph+ ALL. However, the small sample size, the limitation to Italian centers, as well as unclarity of how the study population relates to any external population, contributes to concerns relating to generalizability of the reported results.

Secondary endpoints

In the primary CSR, it is noted that the Kaplan-Meier curve for duration of CMR has a number of events from month 30 and forward that do not appear to be reflected on the duration of CHR curve, which has no events (but several participants censored) from month 30 and forward. In addition, it is noted, in CSR Addendum, that the median duration of CMR is 14.06 months (95% CI: 6.24, 21.91), which is noticeably shorter than median duration of CHR that is reported to be 49.94 months (95% CI: 20.70, NE). The MAH explains that hematologic responses are attained more rapidly than the deeper responses, and that a time lag between loss of molecular response and loss of hematologic response is expected since the molecular assessment of response is more sensitive than morphologic assessment of blood cell counts.

With a median follow-up of 44.9 months at the initial data cut-off date 24 APR 2020, the median duration of CHR had not been reached. In the CSR Addendum, with a longer follow-up as of 30 SEP 2021 data cut-off date, the median duration of CHR was reported to be 49.94 months (95% CI: 20.70, NE). Further, the median EFS was estimated to 14.31 months (95% CI: 9.30, 22.31) at the initial data cut-off date, and prolonged to 29.54 months (95% CI: 18.27, 60.32) at the final data cut-off date, as reported by the MAH. Taken at face value, these results are indicative of a clinically relevant effect size.

However, it is noted a plateau-like shape of the Kaplan-Meier curves in CSR Addendum (data cut-off date of 30 SEP 2021) for both duration of CHR and EFS, which raised questions. The EFS curve has no events between month 35 to 50, but then several events from month 50 to 65. The duration of CHR curve has a similarly plateau from month 30 to 45, and then several participants are censored from month 50 to 65. The MAH confirmed that the steeper slope in the EFS curve from month 50 and forward (according to which all patients had had an event) was due to discontinuation of ponatinib in several participants, and that these participants were then simultaneously censored on the curve for duration of CHR. However, this is an odd cause of censoring in a duration of response analysis. Overall, the inclusion of treatment discontinuation as an event in the EFS analysis is absurd, as it indicates that being on treatment is a patient benefit per se.

Thus, to clarify the background and substantiate the form of these curves (duration of CHR and EFS curve), and enable an adequate assessment, the MAH was asked to present the nature of the EFS events, to elucidate how different events were distributed over time. By now, the MAH has thoroughly presented events before and after month 30 (CHR) and before month 30 and after

month 50 (EFS). For CHR, in principle all events occurred ≤ month 30 while there was only one recorded event after month 30. The MAH considers that the plateau of the duration of the CHR curve indicates that hematologic responses were durable once maintained for > 30 months. For EFS, almost all events in the KM curve occurring from Month 50 onward were related to duration of study follow-up at the time of study completion. In estimating the EFS curve censoring subjects at last assessment/study discontinuation its shape should appear similar to the CHR duration KM curve and instead of a plateau rather witness of that no or only very few ("true") events were observed beyond month 30. Even if it is considered clinically plausible that hematologic responses are durable once maintained for > 30 months, the lack in recorded events after approximately 30 months raise concern regarding follow-up reliability. The updated analyses provided in the CSR addendum are thus acknowledged, however, the presentation of CHR duration in 5.1 in the SmPC should rely on the primary analysis outcome as provided in the primary CSR.

The MAH has clarified that all participants who achieved CHR did so before Week 24. Further, a swimmer plot was presented to illustrate the duration of ponatinib treatment in, including the reason for discontinuation, the duration of hematologic response, the occurrence of HSCT, and study follow-up for each participant.

Among the 6 participants with CNS disease at baseline, all achieved CHR at Week 6. Of note, one of these participants (047001) discontinued from the extension phase due to hematologic and extramedullary relapse on Day 421 but had an event date for the analysis of duration of hematologic response first on Day 575 after death due to cardiovascular disease. The MAH should clarify the handling of this participant, and explain why loss of response was not assigned at day 421**.**

The estimated 2-year OS probability was approximately 68% (as interpreted by the assessor). This time dependent endpoint does not isolate a treatment effect in a single-arm trial.

Summary of main study(ies)

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

Table 21 Summary of Efficacy for trial INCB 84344-201

Title: Front-line treatment of Philadelphia positive (Ph+)/BCR-ABL positive acute lymphoblastic leukemia (ALL) with ponatinib, a new tyrosine kinase inhibitor (TKI). A Phase 2 exploratory multicentric study in patients more than 60 years old or unfit for a program of intensive chemotherapy and stem cell transplantation.		
Study identifier	www.clinicaltrials.gov NCT01641107, EudraCT 2012-002761-35, GIMEMA LAL1811	
Design	Single-arm, open-label, phase 2 study, multicenter, 22 sites in Italy	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Steroid pre-treatment for 7 to 14 days, then ponatinib treatment for 48 weeks. Not applicable After the main phase, followed by 2 years extension phase, if they benefited from the study drug, until disease relapse or progression.
Hypothesis	Exploratory: The hypothesis tested was that 75% of participants using ponatinib would be in CHR at 6 months.	
Treatments group	Single-arm study including Ph+ ALL patients	Study core (main) phase: steroid pre-treatment for 7 to 14 days, followed by ponatinib treatment 45 mg/day for 6 weeks (defined as one course) for 8 courses.

<table>
<tr><td rowspan="4">Endpoints and definitions</td><td>Primary: Complete hematologic response at 6 months</td><td>CHR at 6 months</td><td>The proportion of participants who were in CHR at 6 months.</td></tr>
<tr><td>Secondary, as defined in the SAP: Median duration of CHR</td><td>CHR</td><td>Duration of CHR defined as the date of achievement of CHR to the date of CHR loss.</td></tr>
<tr><td>Secondary: Event-free survival</td><td>EFS</td><td>The length of time from the date of enrollment (date of steroid first dose) to the date of the event. Event was defined as:
– Failure of achieving CHR at Week 6
– Treatment discontinuation
– CHR lost
– Death by any cause</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Database lock</td><td colspan="3">Data cut-off 24 APR 2020 (primary CSR). Data cut-off 30 SEP 2021 (CSR Addendum)</td></tr>
<tr><td colspan="4">Results and Analysis</td></tr>
<tr><td>Analysis description</td><td colspan="3">Primary Analysis (Primary CSR and CSR Addendum)</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="3">The full analysis set included all participants enrolled (n=44) in the study who received at least 1 dose of study drug.</td></tr>
<tr><td rowspan="9">Descriptive statistics and estimate variability</td><td>Treatment group</td><td colspan="2">Ph+ ALL</td></tr>
<tr><td>Number of subjects</td><td colspan="2">44</td></tr>
<tr><td>CHR at 6 months, % (n), (Primary CSR)</td><td colspan="2">86.4 (38)</td></tr>
<tr><td>(95% CI)</td><td colspan="2">(72.6, 94.8)</td></tr>
<tr><td>Median duration of CHR, months (CSR Addendum)</td><td colspan="2">49.94</td></tr>
<tr><td>(95% CI)</td><td colspan="2">(20.7, NE)</td></tr>
<tr><td>Median EFS, months, (CSR Addendum)</td><td colspan="2">29.5</td></tr>
<tr><td>(95% CI)</td><td colspan="2">(18.3, 60.3)</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>Notes</td><td colspan="3">The analyses of efficacy measures are descriptive, and no formal statistical tests were performed.</td></tr>
</table>

3.4.3. Matching-Adjusted Indirect Comparison (MAIC)

In addition to the two single-arm studies (INCB 84344-201 and AP24534-11-001), a systematic literature review and an indirect treatment comparison were conducted to compare ponatinib against imatinib as a first-line treatment option. This is described in the submitted report "Ponatinib vs. Imatinib as First-line Treatment for Philadelphia Chromosome-positive Acute Lymphoblastic Leukaemia" (EVG-30650-03, 21 April 2022, Version 4.0).

Assessor's comment:

These indirect treatment comparisons using historical controls were not pre-planned. This should however be considered given the fact that both studies pertinent to the sought indications were initially, and in one instance, still is, investigator sponsored. They are nonetheless appreciated and in line with advice received (MPA, 18 November 2020) and should have been performed in an attempt to address challenges that comes with single-arm trials. For firm conclusions on the relative efficacy of ponatinib versus imatinib in the first line setting it is expected that a randomised study will be required. These indirect treatment comparisons may be useful in putting the ponatinib outcomes from the two SATs into context.

However, currently the comparisons versus imatinib are considered less useful since a major concern is to what extent study AP24534-11-001 and study INCB 84344-201 own external validity.

Objective

The objective was to conduct a matching-adjusted indirect comparison (MAIC) of ponatinib + hyper-CVAD or ponatinib monotherapy compared to an imatinib-based regimen leveraging patient level data from the MDACC (Jabbour) and GIMEMA LAL1811 studies (i.e., study AP24534-11-001 and study INCB 84344-201) on overall survival (OS), event-free survival (EFS), disease-free survival (DFS), complete haematologic response (CHR), molecular response including major molecular response (MMolR) and complete molecular response (CMR), discontinuation due to adverse events (AE) and death due to AEs.

Method for Comparability Assessment

The comparability of the MDACC (Jabbour) and GIMEMA LAL1811 studies against imatinib studies was to be evaluated based on:

• Overall study design features, such as duration of the follow-up

• The study inclusion and exclusion criteria

• The definition of the endpoints of interest:

o OS

o EFS

o Disease-free survival (DFS)

o Overall remission rates (ORR), including complete (CR)/complete haematologic response (CHR) and partial remission (PR)/partial haematologic response (PHR)

o Molecular response: molecular complete response (MCR) and major molecular response (MMolR)

o Cytogenetic response: complete cytogenetic response (CCyR)

o Proportion of patients discontinuing treatment due to adverse events (AEs)

o Proportion of patients with grade III-IV AEs

o Proportion of patients who die because of an AE

• Overlap in characteristics of the MDACC (Jabbour) and GIMEMA LAL1811 and imatinib populations; in particular, the possibility of conducting an MAIC using data from a subgroup of the MDACC (Jabbour) and GIMEMA LAL1811 studies that more closely matches a population reported in an imatinib study will be explored.

As the MDACC (Jabbour) and the GIMEMA LAL1811 study are both single-arm, unanchored MAICs were used to estimate the relative efficacy and safety between treatments.

The MAIC was conducted using the methods described by Signorovitch and colleagues (*Signorovitch JE, Sikirica V, Erder MH, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value Health. 2012;15(6):940-947*) following the guidelines of the National Institute for Health and Care Excellence (NICE) (*Phillippo DM, Ades AE, Dias S, et al. Technical Support Document 18: Methods for Population-adjusted Indirect Comparisons in Submissions to NICE. http://www.nicedsu.org.uk/wp-content/uploads/2017/05/Population-adjustment-TSD-FINAL.pdf. Published 2016. Accessed*)

As the MDACC Jabbour) and GIMEMA studies were single-arm studies, the NICE guidelines required that all known and available prognostic factors and effect modifiers be included in the population-adjustment.

Clinical experts were consulted to understand the key prognostic factors and effect-modifiers: they emphasised that population-adjustment should try to balance, at a minimum, patient's age, Eastern Cooperative Oncology Group (ECOG) PS, white blood cell (WBC) count, and type of transcript at baseline between included populations.

Assessor's comment:

The MAH followed the guidelines of the National Institute for Health and Care Excellence (NICE). Since both index studies are single-arm studies unanchored MAICs were used.

Citing the NICE guideline(s), a number of drawbacks with the unanchored MAIC have been identified including: "An unanchored MAIC ... effectively assumes that absolute outcomes can be predicted from the covariates; that is, it assumes that all effect modifiers and prognostic factors are accounted for. This assumption is very strong, and largely considered impossible to meet. Failure of this assumption leads to an unknown amount of bias in the unanchored estimate."

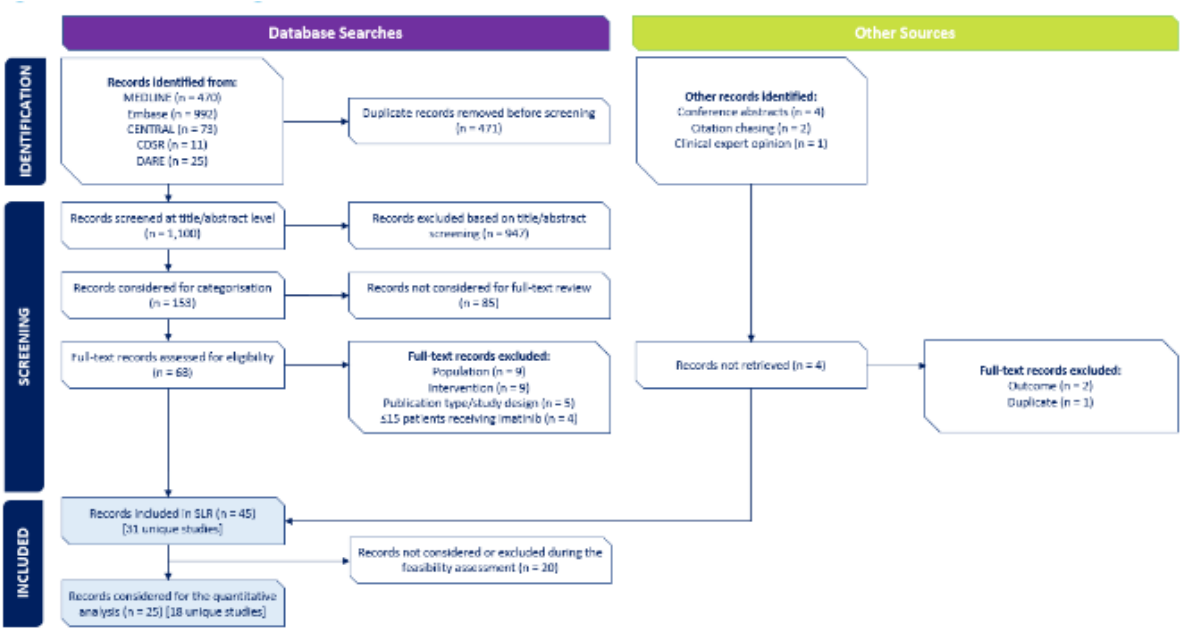
It is notable that CrCL is not available in the control population, despite this being an important predictor of death risk in general.

Systematic literature review (SRL)

According to the SRL protocol (Version 1.2, 23 June 2021), the SLR was to be conducted according to the standards set forth in established guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and the Cochrane Handbook for Systematic Reviews of Interventions) as well as the high-quality standards required by the National Institute for Health and Care Excellence (NICE) and most health technology agencies.

Systematic searches were conducted in MEDLINE, Embase, the Cochrane Library (Cochrane Central Register of Controlled Trials [CENTRAL] and Cochrane Database of Systematic Reviews [CDSR]) and Database of Abstracts of Reviews of Effectiveness (DARE) to identify relevant peer-reviewed studies.

Figure 15 PRISMA Diagram



Abbreviations: CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; DARE = Database of Abstracts of Reviews of Effectiveness; SLR = systematic literature review

Study Selection

The study selection process was conducted in two systematic steps:

- Step 1: Title and abstract screening
- Step 2: Full-text screening

During the study selection, each record was assessed against the eligibility criteria listed in Table 2, which presents the inclusion and exclusion criteria based on the population, interventions and comparisons, outcomes, and study design (PICOS) framework. Ultimately, all of the inclusion criteria and none of the exclusion criteria will need to be met for a study to be eligible for inclusion in the review. No study will be excluded at the title- and abstract-level solely because it provides insufficient information.

Table 22 PICOS Selection Criteria

Domain	Inclusion Criteria	Exclusion Criteria
Population*	Adult patients with newly diagnosed Ph+ ALL who have not received prior systemic therapy**	• Paediatric patients • Ph- ALL • Other leukaemia types
Intervention	The following TKI (alone or in combination with chemotherapy, steroids or stem cell transplantation) • Ponatinib • Imatinib	Studies evaluating other interventions or imatinib/ponatinib in combination with other targeted therapies
Comparison	Any or no comparison	NA
Outcomes	Efficacy: • Overall survival • Event-free survival • Response (complete response / complete hematologic response, complete molecular response, major molecular response, complete cytogenetic response, minimal residual disease) Safety: • Any grade or grade 3+ AE • Any grade or grade 3+ treatment-related AE • Serious AE (any or treatment-related)	Outcomes not of interest
Study Design	• Randomised controlled, single-arm or non-randomised trials (phase II–IV) • Observational/real-world studies • SLRs of relevant studies	• Letters, comments, editorials, notes • Narrative reviews
Sample Size	Studies with ≥15 patients receiving either imatinib or ponatinib	NA

*

*Studies will be included as long as ≥80% of the study population meet the PICOS criteria or if relevant subgroup data are available. This threshold is in line with recommendations by IQWiG4.

** The literature search and title/abstract screening process will not be restricted to first-line therapy to provide Incyte with an overview of all available studies for Ph+ ALL irrespective of line of therapy. However, full-text screening and data extraction will be restricted to first-line therapy only at this stage.

Abbreviations: AE = adverse event; Ph+ ALL = Philadelphia Chromosome positive acute lymphoblastic leukaemia; SLR = systematic literature review; TKI = Tyrosine Kinase Inhibitor

The material identified from the literature review was reviewed and studies identified were divided between studies that included patients who were eligible to high dose therapy (HDT) and SCT and studies that focused on patients non-eligible to HDT and SCT. As such, 15 and 3 studies respectively targeting patients eligible or non-eligible to HDT and SCT were identified.

Assessor's comment:

A protocol (Version 1.2, 23 June 2021) for the SLR has been submitted. The SLR was transparent and appear comprehensive.

The timeframe for the database searches was 2000-present justified by imatinib's first approval for medical use by the EMA and the FDA in 2001. Starting out wide could be wise but going back two decades imply a risk for "drift" while first approval did not comprise first-line treatment.

In the end, 15 and 3 studies respectively targeting the populations fit for purpose were identified from the substantial amount of initial hits. The last step of the actual selection has been accounted

for and implies that 2/15 and 1/3 studies were retained and used for the indirect treatment comparisons versus imatinib in each population, respectively.

Derivation of MAIC Weights

MAIC weights are estimated through propensity score-like regressions. The choice of the covariates included in the regression models is crucial as upon a successful population-adjustment, the populations become comparable for the set of factors included in the adjustment.

As the MDACC (Jabbour) and GIMEMA studies were single-arm studies, the NICE guidelines require that all known and available prognostic factors and effect modifiers be included in the population-adjustment. However, matching on a large list of factors can reduce the final effective sample size (ESS) of the MAIC population, making comparisons technically not feasible or inferences no longer reliable. Therefore, the matching strategy intended to preserve an ESS of at least 15 while adjusting for as many effect modifiers and prognostic factors as needed. Several scenarios were investigated:

Scenario 1: Intended to adjust for all mutually available baseline characteristics among the ponatinib studies and their respective comparator imatinib studies. The list of variables available and similarly defined between the ponatinib and imatinib populations available for the population-adjustment are presented below.

Table 23 Variables Available and Similarly Defined across the Ponatinib and Imatinib Populations Eligible for Inclusion in the Population-adjustment

	GRAAPH-2005	NCT00038610	Ottmann et al., 2007
Age	✓	✓	✓
Sex	✓	✓	✓
Karnofsky performance status or ECOG PS	✓	✓	×
Central nervous system disease at baseline	✓	✓	✓
Type of BCR-ABL transcript (m, M, p190, p210)	✓	✓	✓
Response status at study entry	✓	✓	NA
White blood cells / blast counts at baseline	✓	✓	✓
Haemoglobin levels	×	✓	×
Platelet counts	×	✓	✓
Albumin levels	×	✓	×
LDH levels	×	✓	×

Abbreviations: ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; NA = not applicable; PS = performance status

Scenario 2: Intended to adjust for the list of prognostic factors and effect modifiers as highlighted by clinical expert in Ph+ ALL. The list of such factors is provided in the table below. Tick marks identify factors commonly available and similarly defined in the ponatinib studies and their respective comparator studies.

Table 24 List of Prognostic Factors and Treatment Effect Modifiers in Ph+ ALL Identified by Clinical Experts Available for Inclusion in the Population-adjustment

	GRAAPH-2005	NCT00038610	Ottmann et al., 2007
Age	✓	✓	✓
Karnofsky performance status or ECOG PS	✓	✓	×
Geographical region	×	×	×
Central nervous system disease at baseline	✓	✓	✓
Testicular involvement	×	×	×
Race	×	×	×
Histology (CML in accelerated or blast phase)	×	×	×
Type of BCR-ABL transcript (m, M, p190, p210)	✓	✓	✓
Response status at study entry	✓	✓	NA
WBC/blast counts at baseline	✓	✓	✓
Cytogenetic risk groups (isolated Ph+, Ph+ and other, diploid…)	×	×	×
Deletion of 9p	×	×	×
Presence of +der(22)	×	×	×
Ikaros deletions and recurring lesion (Ikaros + signature)	×	×	×
BCR-ABL1 TKD	×	×	×
Additional chromosome aberration	×	×	×
Pax5, pax5 plus	×	×	×

Abbreviations: CML = chronic myeloid leukaemia; Eastern Cooperative Oncology Group; NA = not applicable; Ph+ = Philadelphia chromosome-positive; PS = performance status; WBC = white blood cell

Scenario 3: Intended to adjust for factors highlighted by clinical experts as needing to be prioritised for a population-adjustment:

o Age

o ECOG PS

o WBC/blast counts at baseline

o Type of BCR-ABL transcript

Below are the five models investigated For the PAIC using data from the GRAAPH-2005 study investigating ponatinib + HCVAD.

Model 1 matched populations on all baseline characteristics available in both trials. The ESS obtained was small, but the model converged.

Model 2 was based on model 1 and matched populations on all baseline characteristics available in both trials. Compared to model 1, model 2 performed a less granular population-adjustment, only retaining an adjustment on grouped range of value (i.e., proportion of patients above a certain threshold value) instead of matching on both medians and grouped range of values. The ESS obtained was higher and the model converged. This model was investigated in a sensitivity analysis.

Model 3 matched populations on clinically validated prognostic factors or treatment effect modifiers in Ph+ ALL. Compared to the two first models, the sex of patients was not included in the population-adjustment. The ESS increased and the model converged. This model is proposed as the **base-case** model and is presented in the body of the report.

Model 4 was based on model 3 and omitted baseline adjustment on WBC count at baseline. This model was intended as a sensitivity analysis as this factor was responsible for the largest drop in the ESS.

Model 5 matched populations on the four factors to prioritise according to clinical experts (age, ECOG PS , WBC count, and type of transcript). The ESS obtained was only marginally higher than the one achieved in the base-case model and thus this model was not investigated further.

Assessor's comment:

As identified in the submitted report, "the choice of the covariates included in the regression models is crucial as upon a successful population-adjustment". Limitations in sample size as well as factors commonly available and similarly defined in the ponatinib studies and their respective comparator studies decided on which model(s) that was to be used. The matching strategy intended to preserve an ESS of at least 15. This appears limited and impacts on power/precision and is evident by wide confidence intervals (below).

Measuring Relative Treatment Effects

Depending on the nature of the outcomes, i.e., TTE (OS, DFS, EFS) or binary (CHR, molecular response, safety), the process differs:

• For TTE outcomes, the relative efficacy estimates were quantified as a hazard ratio (HR) with a 95% confidence interval (CI). The HRs were obtained using a Cox regression analysis fitted on the ponatinib data and the reconstructed individual-patient data (RIPD) of the comparator study used in the matching.7,8 RIPD were generated from digitised coordinates using the algorithm presented by Guyot et al., 2012.9 The assumption of proportional hazards was evaluated by plotting the log-log survival vs. log time after applying the weights.

• For binary outcomes, the relative efficacy estimates were quantified as an odds ratio (OR) with a 95% CI. The OR was obtained using logistic regression analysis fitted on the ponatinib data and the RIPD of the imatinib study used in the matching.

Robust sandwich estimators were used for the calculation of the standard errors (SE). The regression models were fitted using the weighted MDACC (Jabbour)/GIMEMA LAL1811 population and the unweighted MDACC (Jabbour)/GIMEMA LAL1811 data against comparator data so as to estimate the reduction in the bias induced by the population-adjustment.

Assessor's comment:

The analysis methods were standard. Access to comparator study outcome information was limited and needed to be reconstructed.

MAIC results in the HDT-SCT eligible population

Data for the GRAAPH-2005 study were retrieved from Chalandon et al. 2015.12 This study reported OS, EFS, CHR and molecular response (major and complete).

Data for the NCT00038610 study were retrieved from Daver et al. 2015.13 This study reported OS either censoring patients at the time when they received a subsequent SCT or not censoring these patients, DFS, CHR, molecular response (major and complete), death due to AEs and discontinuation due to AEs.

Table 25 Summary of Inclusion of Imatinib Studies Conducted in HDT-SCT Eligible Patients in the PAIC

Study Name	Intervention	Include in the PAIC	Note	Most Appropriate Ponatinib Population
GRAAPH-2005[12]	Induction with imatinib + reduced-intensity chemotherapy vs. induction with hyper-CVAD. Induction followed by an imatinib + methotrexate + cytarabine cycle to bridge to SCT. Up to 8 cycles of treatment alternating imatinib + hyper-CVAD with imatinib + methotrexate + cytarabine for patients not receiving transplant.	Yes	-	MDACC (Jabbour) patients 60 or below with active disease at baseline, not previously treated with TKI
NCT00038610[13,14]/AUS01 in the EMA EPAR / scientific discussion dossier of imatinib[15]	8 induction-consolidation courses of imatinib + hyper-CVAD alternated with imatinib + methotrexate + cytarabine	Yes	-	MDACC (Jabbour) patients not previously treated with TKI

Assessor's comment:

A summary of inclusion of imatinib studies conducted in HDT-SCT eligible patients in the PAIC has been presented for all the 15 studies identified. The Wassmann et al. study was not retained in the MAIC/PAIC analyses since, as clear from the report, treatment was only partially of interest (induction without imatinib) and there were few baseline characteristics reported.

Baseline characteristics

Table 26 presents the baseline characteristics of the weighted MDACC ponatinib + hyper-CVAD populations along their respective comparator imatinib + hyper CVAD populations (from the NCT00038610 and GRAAPH-2005 studies) and the effective sample size achieved in each comparisons conducted in the HDT-eligible populations. The list and modality of factors included in the population-adjustment differs as the reporting of the GRAAPH-2005 and NCT00038610 studies differed.

Table 26 Baseline Characteristics of the Weighted Ponatinib + Hyper-CVAD Populations Following Population Adjustment and Reported Imatinib + Hyper-CVAD Populations from the GRAAPH-2005 and NCT00038610 Studies

	Comparison of MDACC vs. GRAAPH-2005		Comparison of MDACC vs. NCT00038610	
	Weighted ponatinib + hyper-CVAD	Imatinib + hyper-CVAD	Weighted ponatinib + hyper-CVAD	Imatinib + hyper-CVAD
(Effective) Sample size	24.363	133		
Proportion of patients with age ≥30	0.857	0.857	Not included	Not reported
Proportion of patients with age ≥60	0.000	0.000	Not included	Not reported
Median age	Not included	Not included	51	51
Proportion of patients with ECOG PS 0–1	0.842	0.842	Not included	Not reported
Proportion of patients with ECOG PS 0	Not included	Not reported	0.130	0.130
Proportion of patients with ECOG unknown	0.000	0.023	Not included	Not reported
Proportion of patients with CNS disease at baseline	0.023	0.023	0.130	0.130
Proportion of patients with WBC count (10^9/L) 30 or higher	0.414	0.414	0.370	0.370
Proportion of patients with WBC count missing	0.000	0.000	0.000	0.000
Proportion of patients with BCR-ABL1 transcript: m or p190	0.722	0.722	0.667	0.667
Proportion of patients with BCR-ABL1 transcript: missing	0.000	0.010	0.000	0.000
Proportion of patients in CR at start	0.000	0.000	0.009	0.167
Proportion of patients with prior TKI	0.000	0.000	0.000	0.000

Abbreviations: CNS = central nervous system; CR = complete remission; CVAD = cyclophosphamide, vincristine, doxorubicin and dexamethasone; ECOG = Eastern Cooperative Oncology Group; ESS = effective sample size; PS = performance status; TKI = tyrosine kinase inhibitor; WBC = white blood cell

Analyses on the high-dose eligible population

Table 27 presents a summary of the MAIC results in the HDT-SCT eligible population. Bolded rows highlight results with a p-value less than the 0.05 threshold.

Table 27 Summary of the MAIC results in the HDT-SCT eligible population

Outcome	Comparsion	Unadjusted Comparison (95% CI) [p-value]	Population-adjusted Comparison (95% CI) [p-value]
OS	**Ponatinib + hyper-CVAD (MDACC) vs. imatinib + hyper-CVAD (GRAAPH-2005)**	**HR: 0.41 (0.25, 0.68) [<0.001]**	**HR: 0.35 (0.17, 0.74) [0.006]**
	Ponatinib + hyper-CVAD (MDACC) vs. imatinib + hyper-CVAD (NCT00038610) – no censoring of SCT-receiving patients	**HR: 0.42 (0.24, 0.73) [0.002]**	**HR: 0.35 (0.18, 0.70) [0.003]**
	Ponatinib + hyper-CVAD (MDACC) vs. imatinib + hyper-CVAD (NCT00038610) –censoring of SCT-receiving patients	**HR: 0.36 (0.20, 0.63) [<0.001]**	**HR: 0.30 (0.15, 0.59) [0.001]**
EFS	**Ponatinib + hyper-CVAD (MDACC) vs. imatinib + hyper-CVAD (GRAAPH-2005)**	**HR: 0.40 (0.26,0.61) [<0.001]**	**HR: 0.42 (0.21, 0.83) [0.013]**
	Ponatinib + hyper-CVAD (MDACC) vs. imatinib + hyper-CVAD (NCT00038610)	NR	NR
DFS	Ponatinib + hyper-CVAD (MDACC) vs. imatinib + hyper-CVAD (GRAAPH-2005)	NR	NR
	Ponatinib + hyper-CVAD (MDACC) vs. imatinib + hyper-CVAD (NCT00038610)	**HR:0.55 (0.32,0.92) [0.024]**	**HR: 0.50 (0.27, 0.93) [0.029]**
CMR	**Ponatinib + hyper-CVAD (MDACC) vs. imatinib + hyper-CVAD (GRAAPH-2005)**	**OR: 12.34 (5.77, 26.41) [<0.001]**	**OR: 12.11 (3.77, 38.87) [<0.001]**
	Ponatinib + hyper-CVAD (MDACC) vs. imatinib + hyper-CVAD (NCT00038610)	**OR: 4.93 (2.13, 11.39) [<0.001]**	**OR: 5.65 (2.02, 15.76) [<0.001]**
	Ponatinib (GIMEMA LAL1811) vs. imatinib (Ottmann et al., 2007)	**OR: 7.65 (2.48, 23.64) [<0.001]**	**OR: 6.20 (1.60, 24.00) [0.008]**
MR (MMolR+ CMR)	**Ponatinib + hyper-CVAD (MDACC) vs. imatinib + hyper-CVAD (GRAAPH-2005)**	**OR: 4.19 (1.77, 9.93) [0.001]**	**OR: 5.24 (1.79, 15.37) [0.003]**
	Ponatinib + hyper-CVAD (MDACC) vs. imatinib + hyper-CVAD (NCT00038610)	OR: 2.18 (0.77, 6.15) [0.141]	OR: 2.14 (0.55, 8.34) [0.274]
Discontinuation due to AEs	Ponatinib + hyper-CVAD (MDACC) vs. imatinib + hyper-CVAD (GRAAPH-2005)	NR	NR
	Ponatinib + hyper-CVAD (MDACC) vs. imatinib + hyper-CVAD (NCT00038610) – during the 8 induction / consolidation cycles	OR: 7.67 (0.93, 63.57) [0.059]	OR: 5.33 (0.61, 46.53) [0.130]
	Ponatinib + hyper-CVAD (MDACC) vs. imatinib + hyper-CVAD (NCT00038610) – entire treatment	OR: 2.39 (0.88, 6.50) [0.088]	OR: 1.96 (0.66, 5.86) [0.229]
Death due to AEs	Ponatinib + hyper-CVAD (MDACC) vs. imatinib + hyper-CVAD (GRAAPH-2005)	NR	NR
	Ponatinib + hyper-CVAD (MDACC) vs. imatinib + hyper-CVAD (NCT00038610)	OR: 3.23 (0.35, 29.55) [0.299]	OR: 3.22 (0.34, 30.22) [0.306]

Abbreviations: AE = adverse event; CHR = complete haematologic remission; CMR = complete molecular remission; CI = confidence interval; CVAD = cyclophosphamide, vincristine, doxorubicin and dexamethasone; DFS = disease-free survival; EFS = event-free survival; HR = hazard ratio; MMolR = massive molecular response; MR = molecular response; NE = not estimable; NR = not reported; OR = odds ratio; OS = overall survival; SCT = stem-cell transplantation.

Assessor's comment:

Within the MAIC report, a discussion was included highlighting the limitations of each comparison. This is appreciated although adds uncertainties regarding the appropriateness of performed comparisons. Bias cannot be ruled out. No firm conclusions are possible, and outcomes should be interpreted cautiously based also on the uncertainty to what extent study owns external validity. With the caveats in mind, it is noted that the outcomes based on the indirect treatment comparisons imply a difference in efficacy in favour of ponatinib + hyper-CVAD versus imatinib + hyper-CVAD. However, EFS could only be estimated within one of the comparisons (GRAAPH-2005) and it is noted that there were differences in CMR and MR depending on comparison (GRAAPH-2005 and NCT00038610). In addition, it is acknowledged that the differences between unadjusted and population-adjusted comparisons were only minor questioning the appropriateness of the model used, and the importance of the factors actually adjusted for.

Analyses on the HDT-SCT non-eligible population

Clinical expert feedback highlighted that the current clinical practice is to treat patients continuously with imatinib and to start the therapy as soon as possible. As a result, out of the 3 studies identified in the SLR only the Ottmann et al. 2007 study was retained for a comparison versus ponatinib as investigated in the GIMEMA LAL1811 study. Table 28 presents the baseline characteristics of the weighted GIMEMA population along the Ottmann et al. 2007 population.

Table 28 Baseline Characteristics of the Weighted Ponatinib Population Following Population Adjustment and Reported Imatinib Population from the Ottmann et al. 2007 Study

	Weighted ponatinib	Imatinib
(Effective) sample size	16.65	28
Median age	66	66
Proportion of patients with age less than 54	0.000	0.000
Proportion of patients with BCR-ABL1 transcript: p210	0.357	0.357
Proportion of patients with BCR-ABL1 transcript: p190/210	0.000	0.000
Proportion of patients with BCR-ABL1 transcript: Missing	0.0	0.071
Proportion of patients with WBC ≥ 25	0.500	0.500
Proportion of patients with WBC: Missing	0.071	0.071

Abbreviation: WBC = white blood cell

The table below presents a summary of the **MAIC results in the HDT-SCT non-eligible population**. Bolded rows highlight results with a p-value less than the 0.05 threshold.

Table 29 Relative Efficacy Estimates for the Observed and Weighted Ponatinib Monotherapy vs. Imatinib in the HDT-SCT non-eligible population

Outcome	Relative Efficacy of Ponatinib Monotherapy vs. Imatinib (95% CI) [p-value]	
	Unadjusted Comparison	Population-adjusted Comparison
OS	HR: 0.40 (0.20, 0.81) [0.011]	HR: 0.24 (0.09, 0.64) [0.004]
CHR	NE	NE
CMR	OR: 7.65 (2.48, 23.64) [<0.001]	OR: 6.20 (1.60, 24.00) [0.008]

Abbreviations: CHR = complete haemetologic remission; CI = confidence interval; CMR = complete molecular response; HR = hazard ratio; NE = not estimable; OR = odds ratio; OS = overall survival

Assessor's comment:

The primary endpoint in the GIMEMA study was CHR month 6. As reported, all imatinib-treated patients (Ottmann et al., 2007) achieved a CHR and no comparative efficacy estimates could be generated for CHR. In comparison, taking all follow-up time into account and ignoring the primary endpoint time-point, 95.5% of the ponatinib monotherapy achieved a CHR.

The outcomes based on the indirect treatment comparisons imply a difference in efficacy in favour of ponatinib versus imatinib for the two efficacy endpoints analysed (OS and CMR). It is noted that the confidence intervals were wide and here, contrary ponatinib-hyper-CVAD comparisons, there was a difference between unadjusted and population-adjusted estimates. However, bias cannot be ruled out and the outcomes should be interpreted with caution.

3.4.4. Discussion on clinical efficacy

3.4.4.1. Discussion on clinical efficacy - Study AP24534-11-001 – ponatinib as add-on to Hyper-CVAD

3.4.4.1.1. Design and conduct of clinical studies - Study AP24534-11-001

Data to support the sought indication "Iclusig is indicated in newly diagnosed adult patients with Ph+ ALL in combination with chemotherapy" are derived from an investigator-sponsored single-center study conducted at MDACC. It was a single-arm trial to evaluate the efficacy and safety of ponatinib in combination with Hyper-CVAD in newly diagnosed Ph+ ALL.

Eighty six of the 87 participants enrolled in Study AP24534 11 001 had been diagnosed with Ph+ ALL and one participant had been diagnosed with CML transforming into lymphoid blast phase.

Not only previously untreated patients were included in this study, since prior treatment with 1 to 2 courses of chemotherapy with or without other TKIs was allowed at study entry. However, the urgent need to start treatment without delay in patients with newly diagnosed Ph+ ALL is acknowledged, as well as the improbability that 1 to 2 cycles of prior antileukemic treatment would have a significant impact of the key endpoints.

The initial study treatment phase consisted of oral ponatinib in combination with 8 cycles of chemotherapy, alternating between Hyper-CVAD and high-dose methotrexate together with cytarabine. Ponatinib was given at 45 mg per day for 14 days in Cycle 1, and then after amended protocol, the ponatinib dose was reduced to 30 mg daily from Cycle 2, with further reduction to 15 mg daily once a CMR was achieved. In response to RSI, the MAH has clarified that the Protocol was amended to reduce the dose of ponatinib due to the identification of ponatinib dose-related risk of VOE. Further, the MAH states that most participants received ponatinib as per the treatment scheme specified in the Protocol, and proposes to amend the posology wording in the SmPC section 4.2 to align with the study Protocol. In addition, the MAH has clarified the presentation of ponatinib dose reductions during the study in SmPC section 5.1.

However, after response to RSI, the text in the present SmPC with respect to the total number of days for ponatinib treatment in first cycle, i.e, 14 days, has been changed from the original text and thereby must be considered incorrect. Both in the protocol, and in the initially submitted SmPC version, it was stated that ponatinib should med given daily for 14 days during the first 21-day cycle of chemotherapy. But, in the current SmPC section 4.2 it is stated that the recommended starting dose of ponatinib is 45 mg once daily during the first 21-day cycle of chemotherapy. The MAH should reinstate the original posology of ponatinib during the first cycle in SmPC section 4.2. In addition, the same issue should be corrected in SmPC section 5.1, since it is now described that ponatinib was given at "45 mg per day in combination with chemotherapy", instead of "45 mg per day for the first 14 days of cycle 1.

The treatment period was followed by 24 months of maintenance chemotherapy with monthly cycles of vincristine and prednisone, in combination with daily ponatinib at 30 mg in patients with no CMR and at 15 mg in those with CMR. Months 6 and 13 of maintenance were intensification cycles of hyper-CVAD and ponatinib administered. Patients with CMR or not candidates for such intensification could abstain the intensification cycles. Also, patients were allowed to discontinue the intensive chemotherapy during Cycle 1-8 and move to the maintenance phase prior to completion of 8 cycles of chemotherapy.

In response to RSI, the MAH explains that limited information is available in the current dataset, and calculations of the number of participants who received induction/consolidation and maintenance therapy are conservative. Sixty-four participants (74%) did not complete 8 cycles of chemotherapy in the study. To reflect the given treatment in and inform prescribers that a considerable portion of the patients continued to maintenance therapy without completing 8 cycles of hyper-CVAD/MTX plus cytarabine, the MAH is asked to specify in SmPC section 5.1 that only 26% of the patients completed the induction treatment but that also those who discontinued chemotherapy before completion of eight cycles were allowed to enter the maintenance therapy.

After the maintenance period, per investigator discretion if patients were benefitting from therapy, continued ponatinib was permitted. In the response to RSI, the MAH explains that among the 23 participants who completed 8 cycles of hyper-CVAD (conservative data), 11 participants continued receiving ponatinib after the maintenance period, and the majority (8/11) remained on ponatinib treatment for ≥ 12 months. The MAH´s proposal regarding recommended duration of treatment in SmPC section 4.2 is only partly accepted, since the recommendation to consider discontinuing of ponatinib if a complete haematologic response has not occurred by 3 months, is not studied or justified by Study AP24534-11-001.

Further, clarification in SmPC section 5.1 regarding reasons for discontinuation is requested.

In addition to ponatinib and Hyper-CVAD, also intrathecal CNS prophylaxis was to be administered, and CNS directed treatment was given to patients with CNS disease at baseline. After response to RSI, the MAH has added recommendations regarding CNS prophylaxis or treatment as per standard clinical guidelines in the SmPC section 4.2. However, in SmPC section 5.1, somewhat excessive information on given CNS prophylaxis or treatment has been introduced, which needs to be shortened.

However, no information on given rituximab can be found in the SmPC. It is considered necessary to clarify the use of rituximab, to adequately reflect the given treatment. The MAH should describe the use of rituximab in SmPC section 5.1, and preferably also add a statement in section 4.2 that treatment with anti-CD20 antibody in CD20+ patients should follow standard clinical guidelines.

Considering the fact that a clear majority of Ph+ ALL patients are expected to reach a complete hematologic remission after first line treatment, EFS at two years is in principle an endpoint that captures clinical benefit in the present treatment scenario.

While it is recognised that EFS at two years without treatment would be close to 0 in the absence of therapy, the study is a single-arm trial with add-on design. Therefore, neither this nor any other endpoint is capable of isolating the effect of ponatinib over and above hyper-CVAD in the pivotal trial. This is a fundamental deficiency which was pointed out in scientific advice.

The secondary endpoints, including ORR and OS, are clinically meaningful. However, OS is a time dependent endpoint that does not isolate drug effects in a single-arm trial. Therefore, OS data should be removed from SmPC section 5.1.

The MAH´s goal (or, rather the sponsor’s) with the current trial was to achieve a 2-year EFS rate >50%, in view of a historical reference 2-year EFS rate 0.49, from unpublished data, on the combination of hyper-CVAD plus imatinib or dasatinib.

The sample size was not based on any statistical considerations. Rather, it appears to have been estimated from an expected referral pattern and what may have been considered a reasonable study timeframe. Upon request, the MAH clarified that the increased sample size from 60 to 100 participants from protocol version 16 February 2016 was to achieve a more robust set of data and a more comprehensive safety profile. Considering the exploratory study design, the provided rationale is not further questioned.

This study is registered at ClinicalTrials.gov (number NCT01424982). It is, as pointed out by the MAH, still ongoing. According to the above source for which the last update was posted 23 September 2022, the study is still open for recruitment with an estimated enrolment of 100 participants.

At the time of the current data cut-off (14 December 2020), the MAH had described that there were no patients in the current dataset remaining on study treatment. The MAH has now stated that this was not correct and has explained that the CSR noted 45 participants in long-term follow-up based on not having an end-of-study date. However, of those, 24 participants were continuing to receive treatment (i.e., those with no end-of-study date and no follow-up contact date) and 21 participants had received their last dose and were being followed up for safety or survival (i.e., those with no end-of-study date but with a follow-up contact date). The MAH is asked to present an updated and correct table for Participant disposition in study AP24534-11-001.

Initially and based on the above, an issue was raised whether the data set underlying the submitted CSR represented a selection of subjects. By now, the MAH has clarified that there were no selection of subjects and that N=87 represented all subjects (86 participants with newly diagnosed Ph+ ALL and one participant with CML transforming into lymphoid blast phase) that had been enrolled at the 14 DEC 2020 data cut-off date. This issue is considered solved.

However, the sample size in the submitted dossier (n=87) is limited and poses an uncertainty in terms of interpretation of results, including external validity and the possibility to validly compare with any external data.

The analyses of efficacy measures are descriptive, and no formal statistical tests were performed for efficacy endpoints, which is appropriate in this setting.

The SAP describing the analysis presented in the current CSR was prepared post data cut-off after the performance of analyses as laid out in the protocol. However, it should be acknowledged that the origin of an SAP authored by the MAH was regulatory advice (e.g., MPA, April 24, 2018, and, as stated by the MAH, apparently also the FDA). The submitted SAP, version: Final 1.0, is dated 15 June 2020: more than two years later than having met with the MPA. The MAH claimed that the SAP was authored prior to the receipt of patient-level data. This has now been confirmed: the SAP was signed off in JUN 2020, patient level baseline data were received on 06 AUG 2020 while the remaining data were received by 11 FEB 2021. The MAH further claims that there were no data-driven elements implemented in the SAP. The main differences between the SAP and the study protocol version 26 were, as highlighted by the MAH, more primary endpoint (EFS) analysis details. This is acknowledged.

Overall, study integrity and internal validity may be questioned given that 26 different protocol versions were submitted in this dossier from an open label investigator-sponsored, single-centre, single-arm trial.

Although the clarifications provided elucidate the sequence of events, convincingly demonstrating that a study owned internal validity and study integrity was not compromised is difficult, not to say almost impossible under the present circumstances.

The numerous protocol amendments are still a concern and as in any open-label study cannot be considered anything else, but data driven. In addition, analyses have been performed during the study and study outcomes have been published (first results in 2015 (n=37), second analysis in 2018 (n=76)).

Despite the very late date for the SAP, study outcomes could be assessed as outlined in the SAP prepared by the MAH provided the SAP does not imply changes contradictory to how the study was initially planned. However, study conduct is a major concern that is considered to hamper the interpretation of study outcomes.

From protocol version 24, the doses of methotrexate and cytarabine were reduced. However, in response to RSI, the MAH has clarified that, overall, the study participants received methotrexate and cytarabine according to the original Protocol which is also described in SmPC section 5.1. In addition, the MAH has added a recommendation for the management of chemotherapy related toxicity in SmPC section 4.2 and 4.4.

In addition to the two single-arm studies (AP24534-11-001 and INCB 84344-201 described below), a systematic literature review and an indirect treatment comparison were conducted to compare ponatinib against imatinib as a first-line treatment option. Since both index studies are single-arm studies unanchored MAICs were used. These comparisons against historical controls were not pre-planned but are nonetheless appreciated and in line with regulatory advice (MPA, 18 November 2020) and were performed in an attempt to address challenges that comes with single-arm trials. However, the comparisons versus imatinib are considered less useful since currently there exists doubts whether study AP24534-11-001 owns external validity.

3.4.4.1.2. Efficacy data and additional analyses - Study AP24534-11-001

According to the CSR, the predefined analysis population for this study is the enrolled population (n=87). In response to RSI, the MAH has stated that 45 participants were in long-term follow-up of which 24 participants were continuing to receive treatment, and 21 participants had received their last dose and were being followed up for safety or survival, at the time of data cut-off 14 December 2020.

Of note, 18 of 21 the participants that had received 1-2 cycles of prior treatment showed a CR already at baseline.

Based on a data cut-off of 14 DEC 2020 with a median duration of follow-up for EFS of 47 months, 26 patients (29.9%) had an event, the median EFS was not reached, and the 2-year Kaplan-Meier estimated EFS rate (primary endpoint) was 75.1% (95% CI 64.0, 83.2). All 87 participants reached a CR (secondary endpoint) at some time.

The 5-year EFS rate was 68.1%. Similar EFS rates were observed in patients with CNS disease (n=6) as for those without CNS disease. The 5-year OS rate was 73.8%.

These endpoints and outcomes are indicative of clinically relevant efficacy; however, they do not isolate an effect of ponatinib, and the external validity of this small single-center study may be questioned. It is recognised, however, that before the introduction of TKIs in Ph+ ALL treatment, remission rates of 45%-90% with short median durations of responses in the range of approximately 10 months were achieved, with chemotherapy alone (Faderl et al 2000, Liu-Dumlao et al 2012, Ravandi and Kebriaei 2009). In patients aged 18 to 59 years with newly diagnosed Ph+ ALL, treatment with hyper-CVAD plus imatinib resulted in estimated 5-year EFS of 42.2% (Chalandon et al 2015).

In summary, the mechanism of action and the understanding of what could be achieved with chemotherapy alone, indicates that it is very likely that ponatinib has an additive effect to efficacy in the proposed indication. However, no reliable and externally valid metric of this additive effect has been presented.

Considering the proposed indication wording '*Iclusig is indicated in newly diagnosed adult patients with Ph+ ALL in combination with chemotherapy*', the MAH claims that the hyper-CVAD backbone could be considered for extrapolation since hyper-CVAD presents the same efficacy and safety characteristics as other intensive backbone chemotherapies with similar compounds, and the chemotherapeutic drugs used for Ph+ ALL treatment are the same or equivalent drug types used with different schedules and dosages within different regimens. However, various chemotherapy combinations are used in the

treatment of Ph+ ALL, and chemotherapeutic drugs other than those included in hyper-CVAD are currently considered possible options to use in frontline treatment of Ph+ ALL.

It is agreed that the results from the combination with hyper-CVAD can be extrapolated to other intensive backbone chemotherapies. However, results cannot be extrapolated to reduced-intensity chemotherapies, since the patient population, and therefore the safety profile, of ponatinib will differ.

The external validity of the generated data and the relationship between the study population and the proposed target population, remains an unsolved matter.

3.4.4.2. Discussion on clinical efficacy – Study INCB 84344-201 - monotherapy

3.4.4.2.1. Design and conduct of clinical studies - Study INCB 84344-201

Data to support the sought indication "Iclusig is indicated in newly diagnosed adult patients with Ph+ ALL as monotherapy after corticosteroid induction in patients not eligible to receive chemotherapy-based regimens" is based on an initially investigator-sponsored study (GIMEMA consortium) for which the sponsorship was later transferred to Incyte. This was a multi-center study (22 study centers in Italy), single-arm, open-label, phase 2 study of oral ponatinib in patients with previously untreated Ph+ ALL ≥ 60 years old or deemed at baseline not fit for intensive chemotherapy and SCT.

The study included patients with Ph+ ALL and no prior history of CML. Inclusion criteria comprised WHO performance status 0-2, and either age ≥ 60 years or age ≥ 18 years, but unfit for program of intensive therapy and allogeneic SCT.

The wording 'unfit for program of intensive therapy and allogeneic SCT' in the inclusion criteria is not fully aligned with the initially sought indication, in which the wording was instead 'not eligible to receive chemotherapy-based regimens', that implies a target population consisting of patients that are not at all expected to be chemotherapy candidates. The MAH has amended its claim to those "unfit for intensive chemotherapy and allogeneic stem cell transplant".

It remains, however, that, the target population of the sought indication may consist of more frail patients than those patents included in the study. The MAH still needs to justify the external validity of the generated data with regard to the relationship between the very small, all-Italian study population and the proposed target population as described by the therapeutic indication.

The study core phase comprised of steroid pre-treatment 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. In participants with CNS disease at baseline, intrathecal therapy was performed with a more frequent dosing schedule, according to the protocol. All participants were to receive daily ponatinib at a dose of 45 mg/day for 6 weeks (defined as one course) for 8 courses, with the same dose and schedule, for a total of 48 weeks.

Each participant was to be treated for a minimum of 6 weeks, after which "patients (*sic*) could be discontinued" in the following situations (i) Lack of CHR at the end of the first course (6 weeks), or (ii) Lack of CCgR, at the end of the third course (18 weeks) (this was planned but not measured), or (iii) Loss of CHR or CCgR, at any time. In response to RSI, the MAH has clarified that the protocol only specified that participants should be treated for a minimum of 6 weeks and could continue treatment in the above-described situations (i) to (iii); that is, discontinuation would be optional at the discretion of the investigator. Thus, the continuation of treatment with ponatinib in some cases corresponding to these criteria is still in line with the protocol, according to the MAH. It is noted that treatment

discontinuation is an EFS event. This does not seem appropriate, but the pre-specification is conservative.

Further, the MAH has clarified that although the criterion regarding "Lack of CCgR, at the end of the third course (18 weeks)" for possible discontinuation was specified in the protocol, no cytogenetic assessments were planned in the protocol at Week 18. Thus, no assessment data are available, and this analysis was not performed. In addition, the MAH has reported that no participant discontinued from ponatinib for not having reached CCgR at the subsequent timepoint when this analysis was performed (i.e., Week 24).

After 48 weeks, participants could continue the treatment for at least another 2 years (extension phase of the study), if they benefited from the study drug, until disease relapse or progression. Alternatively, participants were allowed to receive any treatment that was in their interests. In response to RSI, the MAH has proposed a wording in SmPC section 4.2 regarding the recommended duration of treatment that is only partly accepted, since the recommendation to consider discontinuing of ponatinib if a complete haematologic response has not occurred by 3 months, is not studied or justified by Study INCB 84344-201.

Regarding the posology, in SmPC section 4.2 it is written that 'the recommended starting dose is 45 mg ponatinib daily with reduction to 15 mg daily once CMR is achieved'. This posology with recommendation of dose reduction after achieved CMR does not correspond to the dosage used in the study protocol, which is instead 45 mg daily with dose reduction only in case of grade 3 or 4 adverse events. In response to the RSI, the MAH has clarified that in the context of the safety concerns under evaluation during the study, and in the absence of mandatory dose reductions in the protocol, the investigators were instructed to consider dose reductions as a precautionary measure based on assessment of an individual participant's response to treatment, in addition to the protocol-mandated mandatory dose reductions due to toxicity. Accordingly, the majority of participants (77.3%) had dose reductions during the study, and the proposed posology with regarding dose reductions is acceptable.

The MAH has added recommendations regarding CNS prophylaxis or treatment as per standard clinical guidelines in the SmPC section 4.2. However, in SmPC section 5.1, excessively detailed information on given CNS prophylaxis or treatment has been introduced and needs to be shortened**.**

CHR at 6 months as the primary endpoint, can be accepted in principle, since the study design and CHR endpoint allow for the isolation of an effect of ponatinib, despite the single-arm design of the study (steroids alone would be anticipated to contribute negligibly to efficacy at 6 months).

However, according to ESMO Guidelines 2016, achievement of CMR is the most relevant independent prognostic factor for disease-free survival and OS in ALL, since patients with CMR after induction therapy in several studies have shown significantly superior outcomes compared to patients not reaching CMR. Further, according to ESMO Guidelines, the goal of induction therapy in ALL is the achievement of a CR, or even better, a molecular complete remission/good molecular response, usually evaluated within 6–16 weeks from start of chemotherapy, after which time the achievement of molecular CR is rather uncommon. The MAH has explained that CMR was not considered as an appropriate primary endpoint when the original protocol was written in 2012, based on previous experience of the GIMEMA group with only a very low proportion of participants reaching CMR after chemotherapy-free TKI treatment, and assessment of molecular response by BCR-ABL transcript levels in Ph+ ALL was not yet firmly established as an endpoint at that time. Further, the MAH has explained that the timepoint for the evaluation of the primary endpoint was selected to provide assessment of the durability of the responses.

The pre-defined secondary endpoints including EFS and OS are time dependent endpoints that are considered unsuitable to isolate drug effects in a single-arm trial. Thus, this data needs to be

interpreted with caution in this setting. The MAH is, again, asked to remove EFS and OS data from SmPC section 5.1.

Unlike the pre-defined endpoints in the protocol, duration of CHR was not included as an objective or endpoint in the protocol. Rather, it was planned as an efficacy endpoint in the SAP that was written more than three years after last participant enrolled. Endpoints introduced late during a study raise concerns regarding changes being data driven. In this case, it could be agreed that duration of CHR is in alignment with the primary objective (further, see below). The MAH is now presenting a Kaplan-Meier plot of duration of CHR in the SmPC section 5.1.

Further, it is noted that both in the SAP and in the CSR, the MAH states that the secondary endpoint failure-free survival was planned but not estimated as the cytogenetic response was not measured at week 18. However, according to the protocol section 9.3, failure-free survival is measured in all patients from the date of enrollment, and failure is defined as (i) failure of achieving CHR or loss of CHR, or (ii) death by any causes. Thus, according to the protocol, cytogenetic response is not needed to estimate failure-free survival, as implied in the SAP and in the CSR.

Regarding the secondary endpoints on mutation development, which was requested at scientific advice Nov 2020, the MAH states that endpoints were planned in the protocol, but following the transfer of study sponsorship from GIMEMA to Incyte on 30 JUL 2019, Incyte decided not to continue to explore these parameters because, at this time, the participants were very advanced in terms of study treatment and follow-up and the data were incomplete, and therefore no conclusions could be drawn. In the response to RSI, the MAH has clarified that available mutational analysis data from both from Studies INCB 84344-201 and AP24534-11-001 are sparse and does not allow any firm conclusions.

The study hypothesis underlying the sample size calculation, was that 75% of subjects using ponatinib would be in CHR at 6 months (primary endpoint). The null hypothesis, to be rejected in favour of the alternative, was based on a reference with CHR rate of 55% at 6 months with imatinib treatment (Vignetti et al 2007), as reported by the MAH. However, the primary objective of this study stated that; "Since in these patients, the rate of CHR with other TKI is already closed to 100%, but the relapse rate *at 1 year is 50% or more*, the purpose of this study is to induce better and longer remissions". The misalignment of the primary endpoint and primary objective serves to highlight the exploratory nature of the present study.

The sample size estimation can be followed given the assumptions made for the primary endpoint. The sample size is nevertheless very limited and poses an uncertainty in terms of interpretation of results beyond the primary endpoint. The small sample size contributes to concerns relating to generalizability of the reported results, in turn related to the potential selection of patients given the study design. It is not clear that external validity can be ascertained based on such a small sample size.

Overall, the analysis as outlined in the SAP is acceptable. However, the open label nature of the study without an adequate control in a small number of patients is a major limitation. As in any open-label study, it will not have been possible to ensure that subjective assessments and decisions were not affected by knowledge of treatment.

The full analysis set (n=44) included all participants enrolled in the study who received at least 1 dose of study drug.

All participants were enrolled under the Protocol Amendment #1 dated 07 JUL 2014. The study enrolled participants from 04 DEC 2014 to 24 JAN 2017. Two and a half year after finished enrollment, Incyte became the sponsor from 30 JUL 2019.

The MAH reports that a number of changes in the conduct of the study took place in addition to the protocol amendments. For example, treatment compliance was planned in the protocol, but drug

compliance and drug accountability data were not collected during the GIMEMA sponsorship and were implemented first when Incyte became the sponsor two and a half year after finished enrollment. This issue is considered to reinforce the uncertainty of the external validity study results.

Prior and concomitant medications and post-therapy medications were not captured in the GIMEMA eCRF but were requested to be recorded in the Incyte eCRF, and at the date of cutoff the data were not fully complete. Overall, according to available data, the patients who underwent allo-HSCT or other antileukemic treatment (above ponatinib) had no significant impact on analysis of the primary endpoint. However, one participant (006001) was handled according to a treatment strategy estimand. This participant was classified as a success in the primary endpoint analysis based on assessment at Week 20 (instead of Week 24 which was the prespecified timepoint for primary endpoint analysis), and then subsequently discontinued treatment with ponatinib to start treatment with another antileukemic therapy (blinatumomab) followed by allo-HSCT.

Further, before sponsorship change to Incyte, three "Treatment Advisory Committee" representatives (from Bologna site and GIMEMA) reviewed the complete safety and efficacy data of 27 participants that had started the extension phase upon the data information at the time the change of the sponsorship 30 JUL 2019. No formal documentation on the Treatment advisory committee meetings were made available by GIMEMA at time of the sponsorship change. The MAH was asked to clarify if Incyte had any insight in the available study results when Protocol Amendment 3 dated 15 October 2019 was written, or when the original SAP dated 12 March 2020 was written, and describe which data driven elements that were implemented in the SAP. In reply, the MAH claims that the SAP reflects the analyses planned by GIMEMA and that the SAP was not informed by any data-driven elements. The MAH further states that they only received access to the clinical database after completion of the change in sponsorship on 30 JUL 2019. When the database was transferred, no additional data analysis was conducted between the ASH Annual Meeting in 2017 and the analysis that was conducted for the CSR in AUG 2021.

The original version of the SAP was finalised 12 MAR 2020 prior to database lock (04 MAY 2020) and will have been based on Protocol Amendment (Version) 2 (30 JUL 2019). A protocol version 3 was prepared although was never implemented. The MAH further states that there were no major changes to study conduct or planned analyses.

Taken together, the MAH has provided dates which clarifies the sequence of events. No new concern is raised. However, to convincingly demonstrate that the integrity of a study was not compromised is difficult, if not impossible given the present circumstances. This is not further pursued.

The MAH has been transparent with that there were certain objectives and endpoints planned in the protocol for which it was decided not to investigate further following the transfer of study sponsorship from GIMEMA to Incyte on 30 JUL 2019. According to the MAH, this was because at the time the participants were very advanced in terms of study treatment and follow-up and the data were incomplete, and therefore no conclusions could be drawn. Besides concern over data quality, it cannot be ignored that the reason for data being incomplete may have been correlated with a patient's outcome, and thus, that data missing was not missing at random.

The MAH reports that no protocol deviations significantly affected the completeness, accuracy, and/or reliability of the study data or affected the study conclusions. However, protocol deviations were not collected in the database in the eCRF; the Incyte eCRF only captured reported eligibility criteria deviations. In the eCRF, a total of 2 participants were included in the study even though they did not meet inclusion criterion on adequate pancreatic function. Further, six patients had confirmed ponatinib dose re-escalations after a dose decrease, which was not allowed during the study. These deviations were not reported in the general deviation tracker. Global Protocol deviations were to be reported for

the Treatment advisory committee for which no formal documentation was made available to Incyte at time of sponsorship change. The MAH states that the overall protocol deviations were captured separately by Incyte's representative. The management of protocol deviations is considered to bring additional uncertainty to the generated data.

According to the protocol, the study duration (enrolment + therapy duration + follow-up) was approximately 5 years. The study enrolled participants until 24 JAN 2017. Sponsor decision for study closure was made 30 SEP 2021.

3.4.4.2.2. Efficacy data and additional analyses - Study INCB 84344-201 - monotherapy

Data is presented in a primary CSR from the date of the first participant enrolled (04 DEC 2014) to an initial data cut-off date of 24 APR 2020.

In addition, data up to study completion (final cut-off date 30 SEP 2021) is reported in a separate CSR Addendum. The updated data include evaluation of median duration of CHR, median duration of CCyR, and median OS (all of which had not previously been reached); and also updates to median duration of CMR and median EFS.

In the CSR addendum section ERRATA, the MAH states that the primary CSR incorrectly reported that 11 participants had completed the extension phase at the initial data cutoff date of 24 APR 2020. However, 10 of these participants remained in the extension phase and their status was incorrectly imputed as "completed". In response to RSI, the MAH has presented an updated and correct figure for participant disposition from the CSR Addendum, and the assessment report has been updated.

It is noted that eight participants (18%) did actually receive SCT as post-ponatinib therapy (according to ad-hoc analysis in CSR Addendum), despite the inclusion criteria 'unfit for program of intensive therapy and allogeneic SCT'. This observation brings additional uncertainty to the external validity of the study.

According to the protocol, the hypothesis tested was that 75% of participants using ponatinib would be in CHR at 6 months, as compared to 55% of participants shown to be in CHR at 6 months with imatinib (Vignetti et al 2007). Based on the initial data cut-off date of 24 APR 2020, 38 of the 44 participants (86.4%) were in CHR at 6 months. It is noted that 40,9% of the participants were in CMR at the same timepoint, and 54.5% were in CCgR. It is also noted that the proportion of participants in CHR at week 48 was 56%, which does not obviously fulfill the primary objective presented in the protocol, i.e., to induce better and longer remissions than a relapse rate of 50% at 1 year.

In the CSR Addendum, it is noted a clear discrepancy between the response durability in CMR vs CHR. The median duration of CMR is 14.06 months (95% CI: 6.24, 21.91), which is noticeably shorter than median duration of CHR that is reported to be 49.94 months (95% CI: 20.70, NE). In response to RSI, the MAH states that hematologic responses are attained more rapidly than the deeper responses, and that a time lag between loss of molecular response and loss of hematologic response is expected since the molecular assessment of response is more sensitive than morphologic assessment of blood cell counts.

With a median follow-up of 44.9 months at the initial data cut-off date 24 APR 2020, the median duration of CHR had not been reached. In the CSR Addendum, with a longer follow-up as of 30 SEP 2021 data cut-off date, the median duration of CHR was reported to be 49.94 months (95% CI: 20.70, NE). Further, the median EFS was estimated to 14.31 months (95% CI: 9.30, 22.31) at the initial data cut-off date, and prolonged to 29.54 months (95% CI: 18.27, 60.32) at the final data cut-off date, as reported by the MAH. Taken at face value, these results are indicative of a clinically relevant effect size.

However, it was noted a plateau-like shape of the Kaplan-Meier curves in CSR Addendum (data cut-off date of 30 SEP 2021) for both duration of CHR and EFS, which raised questions. The EFS curve has no events between month 35 to 50, but then several events from month 50 to 65. The duration of CHR curve had a similarly plateau from month 30 to 45, and then several participants were censored from month 50 to 65. The MAH confirmed that the steeper slope in the EFS curve from month 50 and forward (according to which all patients had had an event) was due to discontinuation of ponatinib in several participants, and that these participants were then simultaneously censored on the curve for duration of CHR. However, this is an odd cause of censoring in a duration of response analysis. Moreover, the inclusion of treatment discontinuation as an event in the EFS analysis is absurd, as it indicates that being on treatment is a patient benefit per se. For CHR, in principle all events occurred ≤ month 30 while there was only one recorded event after month 30. The MAH considers that the plateau of the duration of the CHR curve indicates that hematologic responses were durable once maintained for > 30 months. Even if agreed as clinically plausible, the lack in recorded events after approximately 30 months raise concern regarding follow-up reliability. Based on uncertainties regarding to what extent long-term follow-up implied systematically monitoring of events and given the setting of a single-arm trial with no comparator, the presentation of CHR duration in the SmPC (section 5.1) should be from the primary analysis/primary CSR and not as currently proposed, based on the updated analysis as shown in the CSR addendum (data cut-off date of 30 SEP 2021).

It was noted that the definition of event for EFS are misaligned between the protocol and the SAP and CSR. In response to RSI, the MAH has clarified that the definition of EFS events was refined in the SAP since all parameters were not consistently assessed during the study as planned in the protocol, in this initially investigator-sponsored study.

The estimated 2-year OS probability was approximately 68% (as interpreted by the assessor). This time dependent endpoint does not isolate a treatment effect in a single-arm trial.

Among the 6 participants with CNS disease at baseline, all achieved CHR at Week 6. Of note, one of these participants (047001) discontinued from the extension phase due to hematologic and extramedullary relapse on Day 421 but had an event date for the analysis of duration of hematologic response first on Day 575 after death due to cardiovascular disease. The MAH should clarify the handling of this participant, and explain why loss of response was not assigned at day 421.

The reported response rates, and the proportion of patients in CHR at 6 months (86%), isolate a drug effect of ponatinib in the studied population with newly diagnosed Ph+ ALL. However, the small sample size, the limitation to Italian centers, as well as unclarity of how the study population relates to any external cohort, contributes to concerns relating to generalizability of the reported results.

Overall, while activity is evident, it is questioned whether an externally valid metric of the efficacy of ponatinib monotherapy is available for any given target population.

3.4.5. Conclusions on the clinical efficacy

Use in combination with chemotherapy

The MAH proposes an indication for newly diagnosed adult patients with Ph+ ALL in combination with chemotherapy. This is based on a single-arm study from a single-center, where ponatinib was added to hyper-CVAD in 67 patients with Ph+ ALL.

In a single-arm study with add-on design, there is no efficacy metric that isolates drug effects. Moreover, some patients in the study received prior treatment with chemotherapy. Further, in this exploratory study, there were multiple protocol amendments despite the open label, including a sample size expansion as well as changed dosing of ponatinib and chemotherapy agents.

For the reasons given above, it is not clear that the experience reported in the single-arm, single-center study can reasonably be compared to any external cohort. While the activity of ponatinib in this disease setting is not questioned, an internally or externally valid metric of the effect size of the test agent cannot be derived based on the data submitted.

Use as monotherapy

Due to the small sample size of the single-arm pivotal trial (N=44), its exploratory nature, as well as the limitation of study conduct to centers in the same country, the relevance of the effect size in Study INCB 84344-201 to any definable population is unclear.

While the activity of ponatinib as monotherapy is not disputed, there is no externally valid metric of its efficacy for any definable target population.

Overall

Efficacy has not been established for either of the proposed indications.

3.5. Clinical safety

3.5.1. Introduction

Background – known safety profile of ponatinib

Ponatinib (Iclusig) is previously approved for use as second-line (2L) TKI treatment of CML and Ph+ ALL, or in patients with CML or Ph+ ALL who have the T315I mutation.

The ADR table and ADR frequencies in Section 4.8 of the currently approved Iclusig SmPC is primarily based on data from Study AP24534-10-201 (PACE), which was the basis for the original approval of Iclusig. Safety data from the dose-optimising OPTIC trial has subsequently been introduced, within a variation procedure, in the description of selected adverse reactions.

- The PACE trial was a single-arm, open-label, trial in CML and Ph+ ALL patients who were resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy. All patients were administered 45 mg of Iclusig once-daily with the possibility of dose de-escalations and dose interruptions followed by dose resumption and re-escalation. Additional recommendations for prospective dose reduction in all chronic phase (CP)-CML patients in the absence of adverse events were introduced in this trial with the aim of reducing the risk of vascular occlusive events. The safety population included 449 patients, of which 32 were Ph+ ALL patients.
- The OPTIC trial was a phase 2, dose-optimisation trial in CP-CML patients whose disease was resistant to at least 2 prior kinase inhibitors or who had the T315I mutation. Patients received one of three starting dosages: 45 mg orally once daily, 30 mg orally once daily, or 15 mg orally once daily. Patients who received a starting dose of 45 mg or 30 mg had a mandatory dose reduction to 15 mg once daily upon achieving ≤ 1% BCR-ABL1. A total of 282 patients received Iclusig: 94 received a starting dose of 45 mg, 94 received a starting dose of 30 mg, and 94 received a starting dose of 15 mg.

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".

Ponatinib is associated with **vascular occlusive events** (VOEs), including arterial occlusive events (AOEs) and venous thromboembolic events (VTEs). In 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. For the currently applied first-line indication, a dose reduction from 45 mg to 30 mg is recommended already in the 2nd cycle of treatment, and a further reduction to 15 mg, once a CMR has been achieved.

Hepatotoxicity (hepatic failure) has been observed during treatment with ponatinib (uncommon). Increases in ALT and AST 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.

In the currently approved **RMP**, the important identified risks of ponatinib treatment include severe infections and VOEs (including AOEs and VTEs).

3.5.2. Patient exposure

3.5.2.1. Clinical studies

The safety results presented in the current variation application are based on two Phase 2 studies:

- Phase 2 Study AP24534-11-001 (Study AP24534-11-001) from 17 Nov. 2011 to the data cut-off date of 14 Dec. 2020
    - A single-center, single-arm, open-label Phase 2 trial to evaluate the long-term efficacy and safety of ponatinib in combination with chemotherapy in Ph+ ALL with patients continuing in follow-up
    - N=87
    - Objective: To evaluate the clinical efficacy (EFS) of hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) given in combination with ponatinib for Ph+ and/or BCR ABL1-positive ALL
    - Treatment:
        - Ponatinib 45 mg once daily 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 (courses 1,3,5 and 7) and high-dose MTX and cytarabine (courses 2,4,6 and 8).

- After 37 participants were treated, the protocol was amended to reduce the dose of ponatinib to 30 mg per day at Cycle 2, with further reduction to 15 mg once a complete molecular response (CMR; defined as absence of quantifiable BCR-ABL1 transcripts) was achieved.
- For patients with CD20 expression at original diagnosis rituximab could be added.
- The treatment period was followed by approximately 24 months of maintenance chemotherapy. A participant could then receive maintenance therapy with ponatinib daily (30 or 15 mg) indefinitely.
- Safety-related dose modifications for ponatinib were permitted for Grade 3 or 4 nonhematologic toxicity. Treatment could be held until the AE severity improved to Grade ≤ 1 and restarted at 30 mg once daily. The dose could be further decreased to 15 mg daily if needed.

- Phase 2 Study INCB 84344-201 (Study INCB 84344-201) from 04 DEC 2014 to the primary data cutoff date of 24 APR 2020 and final cutoff date 30 SEP 2021
  - Multicenter, Phase 2, single-arm, open-label study of oral ponatinib in patients with Ph+ ALL.
  - N=44
  - Objective: To evaluate the therapeutic effects of ponatinib in patients with Ph+ ALL who were ≥ 60 years old or ≥ 18 years old and unfit for intensive therapy program and allogeneic SCT
  - Treatment:
    - Ponatinib 45 mg once daily for 6 weeks (defined as 1 course) for 8 courses (48 weeks, core phase)
    - Prednisone was administered for 7 to 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
    - Intrathecal (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, intrathecal 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.
    - After 48 weeks, participants could continue treatment for at least another 2 years (extension phase of the study) if they benefited from the study treatment until disease relapse or progression.
    - Ponatinib dose reductions (to 30 or 15 mg) were permitted if Grade 3 or 4 AEs occurred. In case of hematologic AEs concerning WBCs, platelets, and haemoglobin, dose reduction was permitted only after CHR was achieved.

- All participants (regardless of whether they continued the ponatinib regimen, underwent a transplant, or moved to a different treatment) were followed up for 24 months after permanent discontinuation of ponatinib for survival, relapse, and safety (deaths and SAEs) data collection.

As the two studies did not target the same patient population and the investigational treatments differed, the data were not pooled. Thus, safety results are described separately for participants with newly diagnosed Ph+ ALL who received ponatinib in combination with hyper-CVAD, and for elderly or frail participants who received ponatinib after induction therapy with steroids.

In Study AP24534-11-001, safety data were analysed using all participants enrolled in the study for whom BCR-ABL1 could be measured, regardless of whether they received the assigned study treatment.

In Study INCB 84344-201, all data were analysed using all enrolled participants who received at least one dose of study treatment.

Further to the two studies, the MAH presented a Matching-Adjusted Indirect Comparison (MAIC), performed to contextualise the safety results from Study AP24534-11-001 by comparing them with data available for imatinib in combination with chemotherapy.

3.5.2.2. Study subject disposition

Enrolment of patients to **Study AP24534-11-001** started in November 2011. There were 87 patients in the safety population. At the time of data cutoff (14 December 2020), there were no patients still on study treatment and 45 patients (51.7%) remained in the long-term follow-up phase.

Enrolment of patients to Study INCB 84344-201 started in December 2014. There were 44 patients in the safety population. The submission included data up to the primary data cutoff of 24 April 2020 and a CSR addendum presented updated results for 10 participants remaining on study treatment and 14 participants in follow-up after 24 April 2020 up to the final data cutoff of 30 Sept 2021. At the time of sponsor decision for study closure (30 SEP 2021), 9 participants were still receiving benefit from ponatinib treatment in the study extension phase. Each of these participants was transitioned to commercial ponatinib at the end of treatment/study visit. At study closure, 12 participants were in follow-up.

Baseline demographic and disease characteristics in the two studies are shown in Table 30 and Table 31 below. In Study AP24534-11-001, the median age for participants was 46.0 years (range: 21-80 years) and 20 participants (23.0%) were aged ≥ 60 years. Gender was balanced and most participants were White (73.6%) and non-Hispanic or Latino (64.4%). In Study INCB 84344-201, the median age was 66.5 years (range: 26-85 years) and 35 participants (79.5%) were aged ≥ 60 years. Overall, gender was balanced. The mean (STD) body mass index was 26.25 kg/m^2 (4.146 kg/m^2).

Disposition of the safety populations for the two studies is shown in Table 32 and Table 33, respectively.

Table 30. Study AP24534-11-001 Demographics and Baseline Characteristics

	Total (N = 87)
Median age in years (range)	46.0 (21-80)
Sex, n (%)	
Male	44 (50.6)
Female	43 (49.4)
Race, n (%)	
Asian	5 (5.7)
Black or African American	6 (6.9)
White	64 (73.6)
Unknown	12 (13.8)
ECOG score, n (%)	
0	22 (25.3)
1	54 (62.1)
2	11 (12.6)
CNS disease, n (%)	
Yes	6 (6.9)
No	81 (93.1)
CD20-positive, n (%)	
Yes	21 (24.1)
No	66 (75.9)
BCR-ABL1 transcript, n (%)	
p190	63 (72.4)
p210	22 (25.3)
Missing	2 (2.3)
Cytogenetics, n (%)[a]	
Diploid	20 (23.0)
Ph+	67 (77.0)

BCR-ABL1 = breakpoint cluster region-Abelson 1; CNS = central nervous system; CSR = Clinical Study Report; ECOG = Eastern Cooperative Oncology Group; Ph+ = Philadelphia chromosome-positive.
Note: Data cutoff date of 14 DEC 2020.
[a] Participants may be counted in more than 1 category.

Table 31. Study INCB 84344-201 Summary of Demographics and Baseline Characteristics

	Total (N = 44)
Median age in years (range)	66.5 (26-85)
Sex, n (%)	
Male	22 (50.0)
Female	22 (50.0)
Body weight at baseline, kg	
n	39
Mean (STD)	72.19 (14.687)
Median (min, max)	70.00 (47.6, 110.0)
Height at baseline, cm	
n	39
Mean (STD)	165.4 (9.26)
Median (min, max)	165.0 (147, 181)
Body mass index at baseline, kg/m^2	
n	39
Mean (STD)	26.25 (4.146)
Median (min, max)	25.00 (19.8, 39.0)

CSR = Clinical Study Report; max = maximum; min = minimum; STD = standard deviation.
Note: Data cutoff date of 30 SEP 2021.

Table 32. Study AP24534 -11-001: Participant Disposition (Data cutoff 14 Dec 2020)

Categories	Hyper-CVAD + Ponatinib N = 87 n (%)
Safety population	87 (100.0)
Reason for participant terminated study	42 (48.3)
Complete withdrawal/revocation by PI	1 (2.4)
Complete withdrawal/revocation by participant	4 (9.5)
Death[a]	10 (23.8)
Lost to follow-up	3 (7.1)
Toxicity/side effects/complications	3 (7.1)
Treatment completed per protocol	11 (26.2)
Other	10 (23.8)
Number of participants who went to transplant	2 (2.3)
Categories of death reason[b]	20 (23.0)
Cardiac event[c]	4 (20.0)
Multiorgan failure/sepsis[d]	4 (20.0)
Other[e]	12 (60.0)
Summary of participants still on treatment	0 (0.0)
Summary of participants in long-term follow-up	45 (51.7)

CSR = clinical study report; hyper-CVAD = hyper-fractionated cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone; PI = principal investigator; TEAE = treatment-emergent adverse event.

Note: Percentages are calculated out of the number of the enrolled population.

Note: The denominator of each subgroup percent is the row of category total number.

Note: The enrolled population is considered the same as the safety population.

Note: Data cutoff date of 14 DEC 2020.

[a] Deaths based on "Reason off Study" column in AP24534-11-001 CSR Listing 16.2.1.2.

[b] Deaths based on "Survival Status" column in AP24534-11-001 CSR Listing 16.2.1.2.

[c] Two events were TEAEs.

[d] Three events were TEAEs.

[e] Other includes complications post-autologous stem cell transplant, post-relapse, post lung cancer, and head injury sustained after fall (TEAE of hemorrhage intercranial).

Table 33. Study INCB 84344-201: Participant Disposition (Data cut-off 30 Sept 2021)

Categories	Total N = 44 n (%)
Treated in core phase	44 (100.0)
Completed core phase	27 (61.4)
Discontinued from core phase primary reason:	17 (38.6)
Death	1 (2.3)
Documented hematological or extramedullary relapse	3 (6.8)
Excess toxicity (incl myelotoxicity, organ failure, and toxic death)	6 (13.6)
Physician decision	6 (13.6)
Other[a]	1 (2.3)
Treated in extension phase	27 (61.4)
Discontinued from treatment in extension phase primary reason:	27 (61.4)[b]
Death	3 (6.8)
Documented hematological or extramedullary relapse	6 (13.6)
Excess toxicity (incl myelotoxicity, organ failure, and toxic death)	3 (6.8)
Physician decision	3 (6.8)
Missing end of extension phase	1 (2.3)[b]
Other	11 (25.0)
Study terminated by sponsor[c]	9 (20.5)
AE	1 (2.3)
Molecular relapse	1 (2.3)

AE = adverse event; CSR = clinical study report.
Note: Data cutoff date of 30 SEP 2021.
a Cytogenetic relapse.
b One participant, who was missing an end of extension phase status, had died during the extension phase of the study and a description and narrative of this death was included in the Study report
c "Study terminated by sponsor" included entries of "Clinical trial is finished, this is the last visit," "Sponsor instruction for study closure," and "Study terminated by sponsor."

3.5.2.3. Exposure to ponatinib

The extent of exposure to ponatinib in the two studies is summarised in Table 34 and Table 35, respectively.

Table 34. Study AP24534 -11-001: Ponatinib Exposure (Enrolled Population) N=87

Variable	Hyper-CVAD + Ponatinib N = 87
Duration of exposure (days)[a]	
Mean (STD)	671.4 (701.63)
Median	398.0
Q1, Q3	136.0, 1064.0
Min, max	7, 2935
Duration of exposure (categorized), n (%)	
< 1 month	3 (3.4)
1 to < 3 months	9 (10.3)
3 to < 6 months	19 (21.8)
6 to < 12 months	10 (11.5)
12 to < 24 months	14 (16.1)
24 to < 36 months	11 (12.6)
≥ 36 months	21 (24.1)
Number of treatment cycles	
Mean (STD)	22.7 (23.49)
Median	14.0
Q1, Q3	5.0, 32.0
Min, max	1, 96
Number of days dosed	
Mean (STD)	608.2 (669.12)
Median	377.0
Q1, Q3	106.0, 841.0
Min, max	7, 2762
Total cumulative dose (mg)	
Mean (STD)	12,584.0 (12,749.58)
Median	8520.0
Q1, Q3	3420.0, 18,690.0
Min, max	270, 52,755
Dose intensity (mg/day)[b]	
Mean (STD)	22.1 (8.99)
Median	18.4
Q1, Q3	15.4, 27.5
Min, max	8, 45

CSR = clinical study report; hyper-CVAD = hyper-fractionated cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone; max = maximum; min = minimum; Q = quartile; STD = standard deviation.

Note: The enrolled population is defined as all participants who receive at least 1 dose of any study drug.

Note: Data cutoff date of 14 DEC 2020.

[a] Duration of exposure = Last dose of study drug – first dose of study drug + 1.

[b] Dose intensity = Total cumulative dose (mg) / Duration of exposure (days).

Table 35. Study INCB 84344-201: Ponatinib Exposure (Full Analysis Set) N=44

Variable	Total N = 44
Duration of ponatinib treatment during core phase, (days)	
Mean (STD)	275.6 (96.10)
Median (min, max)	333.0 (2, 341)
Average daily ponatinib dose during core phase, (mg)	
Mean (STD)	33.04 (10.257)
Median (min, max)	34.16 (10.1, 46.0)[a]
Total reported ponatinib dose during core phase, (mg)	
Mean (STD)	8860.5 (3917.64)
Median (min, max)	8925.0 (90, 15,120)
Duration of ponatinib treatment during the entire study, (days)	
Mean (STD)	753.1 (685.20)
Median (min, max)	415.0 (2, 2324)
Average daily ponatinib dose during the entire study, (mg)	
Mean (STD)	31.26 (10.402)
Median (min, max)	30.47 (13.6, 45.0)
Total reported ponatinib dose during the entire study, (mg)	
Mean (STD)	21039 (19205.9)
Median (min, max)	14100 (90, 73,035)

CSR = clinical study report; max = maximum; min = minimum; STD = standard deviation.
Note: Data cutoff date of 30 SEP 2021.
[a] During the study core phase, 1 participant had total reported dose of 15,120 mg, duration of treatment of 329 days, and an average daily dose of 45.96 mg/day.

Assessor's comment:

In **Study AP24534-11-001** (N=87; ponatinib + hyper CVAD), the median duration of follow-up for OS on all enrolled participants was 45.1 months (95% CI: 36.50, 63.10). The median duration of exposure to ponatinib was 398 days. Approximately half of the participants (n=46) had a duration of exposure ≥ 12 months and approximately one fourth of participants (n=21) had a duration of exposure of ≥ 36 months. The median relative dose intensity was 18.4 mg/day (range 8 – 45 mg/day). Dose interruptions due to TEAEs occurred in 26.4% of patients (see section on TEAS leading to dose modifications below). There was no information of dose reductions from Study AP24534-11-001. However, of note, after the first 37 patients were enrolled, the protocol was amended so that patients received the 45 mg dose for the first 14 days of cycle 1, then the dose was reduced to 30 mg in cycle 2 (each cycle 21 days) and further reduced to 15 mg once a CMR was achieved. This can explain the low dose intensity as compared with the PACE study that was the basis for the original approval, where the median dose intensity was 44 mg.

In **Study INCB 84344-201** (N=44; chemotherapy ineligible patients), the median duration of exposure during the core phase (8 courses à 6 weeks) was 333 days. The median duration during the entire study was 415 days. In this study, there was no general recommendation of dose reduction to

30 mg or 15 mg at CMR, but dose reductions were made only based on tolerability. The average daily dose was 33 mg and 31 mg during the core phase and the entire study, respectively. The median duration of follow-up for OS was 63.2 months.

3.5.3. Adverse events

In Study AP24534-11-001, AEs were coded using **MedDRA v23.0**, and AE severity was graded according to the NCI CTCAE v4.0 and the MDACC Leukaemia Specific Adverse Event Recording and Reporting Guidelines.

In Study INCB 84344-201, AEs were coded using **MedDRA v22.0**, and AE severity was graded using the NCI CTCAE v4.0.

Treatment-emergent AEs (TEAEs) are defined as any AE that occurs after administration of the first dose of treatment and through 30 days after the last dose of any treatment.

Note that in Study AP24534-11-001, investigator-assessed treatment-related TEAEs does not specify the treatment (hyper-CVAD or ponatinib).

Overviews of all TEAEs are shown in Table 36 and Table 37, respectively.

Table 36. Study AP24534 -11-001: Overview of TEAEs (Enrolled Population)

Variable	Hyper-CVAD + Ponatinib N = 87 n (%)
All TEAEs	87 (100.0)
Treatment-related TEAE	78 (89.7)
Serious TEAE	79 (90.8)
Serious treatment-related TEAE	39 (44.8)
Grade 1 TEAE	0
Grade 2 TEAE	3 (3.4)
Grade 3 TEAE	53 (60.9)
Grade 4 TEAE	25 (28.7)
Grade 5 TEAE	6 (6.9)
Grade 3-5 TEAE	84 (96.6)
Grade 3-5 treatment-related TEAE	53 (60.9)
Grade 3-5 serious TEAE	77 (88.5)
Grade 3-5 serious treatment-related TEAE	32 (36.8)
Serious TEAEs leading to treatment discontinuation or dose interruption[a]	40 (46.0)
Serious TEAEs leading to treatment discontinuation[b]	20 (23.0)
Serious TEAEs leading to dose interruption	23 (26.4)
On-study deaths[c]	5 (5.7)

AE = adverse event; CSR = clinical study report; hyper-CVAD = hyper-fractionated cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone; MedDRA = Medical Dictionary for Regulatory Activities, TEAE = treatment-emergent adverse event.
Note: MedDRA v23.0 was used for coding AEs.

Note: TEAE is defined as any AE that occurs after administration of the first dose of any study drug and through 30 days after the last dose of any study drug.
Note: The counts for Grade 1 to 5 categories include participants who have the highest grade in that category, and Grade 3-5 categories include participants whose highest grade is 3 to 5 reported at any time.
Note: Data cutoff date of 14 DEC 2020.
[a] Serious TEAE may be associated with more than 1 type of dose adjustment.
[b] All serious TEAEs with "Drug Withdrawn" as the action taken.
[c] Deaths reported within 30 days of last dose.

Table 37. Study INCB 84344-201: Overview of TEAEs (Full Analysis Set)

Variable	Total N = 44 n (%)
Participants reporting any TEAEs	42 (95.5)
Participants reporting any serious TEAEs	23 (52.3)
Participants reporting any Grade 3 or higher TEAEs	35 (79.5)
Participants reporting any ponatinib treatment-related TEAEs[a]	37 (84.1)
Participants who temporarily interrupted study treatment because of TEAEs	20 (45.5)
Participants who permanently interrupted study treatment because of TEAEs	11 (25.0)
Participants with dose reductions because of TEAEs	21 (47.7)
Participants who had a fatal TEAE	5 (11.4)

AE = adverse event; CSR = clinical study report; TEAE = treatment-emergent adverse event.
Note: MedDRA v22.0 was used for coding AEs.
Note: TEAEs are any AE either reported for the first time or worsening of a pre-existing event after first administration of study drug and within 30 days of the last dose of study drug.
Note: Data cutoff date of 30 SEP 2021.
[a] Treatment-related TEAEs are TEAEs judged as related to ponatinib by the investigator or with a missing causality.

3.5.3.1. Common Adverse events

Study AP24534-11-001 – ponatinib + hyper CVAD

In Study AP24534-11-001, 100% of patients reported at least one TEAE, and 89.7% of patients reported a TEAE that was assessed by the investigator as treatment-related (related treatment not specified, i.e. hyper CVAD or ponatinib). The most common TEAEs occurred in the SOCs of Gastrointestinal disorders (78.2%), Infections and infestations (72.4%), Blood and lymphatic system disorders (70.1%), Nervous system disorders (70.1%), General disorders and administration site conditions (59.8%), and Skin and subcutaneous tissue disorders (54.0%).

The most common TEAEs (reported in > 20% of participants) are summarised by PT in Table 38. The TEAEs reported in > 30% of participants were febrile neutropenia, pyrexia, abdominal pain, headache, nausea, constipation, pneumonia, and diarrhoea.

Table 38. AP24534 -11-001: TEAEs Reported in > 20% of Participants by PT (Enrolled Population)

MedDRA PT	Hyper-CVAD + Ponatinib N = 87 n (%)
Febrile neutropenia	57 (65.5)
Pyrexia	37 (42.5)
Abdominal pain	32 (36.8)
Headache	31 (35.6)
Nausea	31 (35.6)
Constipation	30 (34.5)
Pneumonia	30 (34.5)
Diarrhoea	28 (32.2)
Rash maculo-papular	25 (28.7)
Peripheral sensory neuropathy	24 (27.6)
Vomiting	23 (26.4)
Anxiety	22 (25.3)
Hypertension	21 (24.1)
Skin and subcutaneous tissue disorders - Other	21 (24.1)
Back pain	20 (23.0)
Oedema peripheral	19 (21.8)
Stomatitis	19 (21.8)
Urinary tract infection	19 (21.8)
Infections and infestations – Other	18 (20.7)
Insomnia	18 (20.7)
Nervous system disorders – Other	18 (20.7)
Sepsis	18 (20.7)

AE = adverse event; CSR = clinical study report; hyper-CVAD = hyper-fractionated cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone; MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term; TEAE = treatment-emergent adverse event.
Note: MedDRA v23.0 was used for coding AEs.
Note: TEAE is defined as any AE that occurs after administration of the first dose of any study drug and through 30 days after the last dose of any study drug.
Note: Participants with 1 or more AEs within a level of MedDRA term are counted only once in that level.
Note: Data cutoff date of 14 DEC 2020.

The most common **treatment-related** TEAEs occurred in the SOCs of Gastrointestinal disorders (51 participants, 58.6%), Nervous system disorders (40 participants, 46.0%), and Skin and subcutaneous tissue disorders (36 participants, 41.4%). The most common (reported in ≥ 20% of participants) treatment-related TEAEs by PT were nausea, diarrhoea, maculo-papular rash, peripheral sensory neuropathy, and abdominal pain.

Study INCB 84344-201 – patients aged ≥ 60 years or ineligible for chemotherapy and SCT

In Study INCB 84344-201, 95.5% of patients reported a TEAE, and 84.1% reported a TEAE that was considered treatment-related by the investigator or with a missing causality assessment. The most common TEAEs occurred in the SOCs of Skin and subcutaneous tissue disorders (59.1%), General disorders and administration site conditions (47.7%), Gastrointestinal disorders (43.2%), and Musculoskeletal and connective tissue disorders (43.2%).

The most common TEAEs (reported in > 5 participants) are summarized by PT in Table 39. The TEAEs reported in > 6 participants were rash and asthenia, ALT increased, GGT increased, erythema, headache, and pyrexia.

Table 39. INCB 84344-201: TEAEs Reported in > 5% of Participants by PT (Full Analysis Set)

MedDRA PT	Total N = 44 n (%)
Rash	16 (36.4)
Asthenia	11 (25.0)
ALT increased	8 (18.2)
GGT increased	8 (18.2)
Erythema	7 (15.9)
Headache	7 (15.9)
Pyrexia	7 (15.9)
Constipation	6 (13.6)
Hypertension	6 (13.6)
Pain in extremity	6 (13.6)
Abdominal pain upper	5 (11.4)
Anaemia	5 (11.4)
Chest pain	5 (11.4)
Cough	5 (11.4)
Hyperglycaemia	5 (11.4)

AE = adverse event; ALT = alanine aminotransferase; GGT = gamma-glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term; TEAE = treatment-emergent adverse event.
Note: TEAEs are any AE either reported for the first time or worsening of a pre-existing event after first administration of study drug and within 30 days of the last dose of study drug.
Note: Participants were counted once under each PT.
Note: AEs were coded using MedDRA 22.0.
Note: Data cutoff date of 30 SEP 2021.

TEAEs of Grade 3 or higher severity

In Study AP24534-11-001, Grade ≥ 3 TEAEs were reported for 96.6% of participants. Grade ≥ 3 TEAEs reported in > 10% of participants were febrile neutropenia (64.4%), pneumonia (34.5%), sepsis (20.7%), urinary tract infection (20.7%), infections and infestations – other (17.2%), pancreatitis (12.6%), ALT increased (10.3%), lipase increased (10.3%), and pyrexia (10.3%).

Overall, 30 participants (34.5%) reported a Grade 4 TEAE, which included sepsis (16 participants), lipase increased (4 participants), hypocalcaemia (3 participants), gastrointestinal disorders – other

(colon adenocarcinoma and small ischemic bowel obstruction pneumatosis), acute respiratory distress syndrome, ALT increased, depression, hypokalaemia, lower gastrointestinal haemorrhage, menorrhagia, pancreatitis, platelet count decreased, pneumonia, and respiratory failure (1 participant each). Of these, sepsis (12 participants), lipase increased (2 participants), gastrointestinal disorders – other (small ischemic bowel obstruction pneumatosis), lower gastrointestinal haemorrhage, and menorrhagia (1 participant each) were serious.

Overall, 53 participants (60.9%) reported a **Grade ≥ 3 treatment-related TEAE**. Treatment-related Grade ≥ 3 TEAEs reported in > 5% of participants were ALT increased, lipase increased, and pancreatitis (each 10.3%), febrile neutropenia (9.2%), AST increased (6.9%), and abdominal pain, hypokalemia, and pneumonia (each 5.7%). Grade 4 treatment-related TEAEs were lipase increased (4 participants), hypocalcemia (2 participants), acute respiratory distress syndrome, ALT increased, sepsis, gastrointestinal disorders – other (small ischemic bowel obstruction pneumatosis), hypokalemia, and pancreatitis (1 participant each). Grade 5 treatment-related TEAEs are discussed below.

In Study INCB 84344-201, Grade ≥ 3 TEAEs were reported for 79.5% of participants. Grade ≥ 3 TEAEs reported in > 5% of participants were GGT increased (reported in 4 [9.1%] participants), acute coronary syndrome, ALT increased, anaemia, hypertension, rash, and skin exfoliation, each reported in 3 participants (6.8%).

Overall, 7 participants (15.9%) reported a Grade 4 TEAE, which included myocardial ischemia, multiple organ dysfunction syndrome, enterococcal sepsis, escherichia sepsis, staphylococcal sepsis, ALT increased, vascular graft occlusion, transaminases increased, WBC count decreased, neoplasms benign, malignant, and unspecified (including cysts and polyps), lung adenocarcinoma, cerebrovascular accident, acute kidney injury, and embolism (1 participant each). Of these, transaminases increased and WBC count decreased were not considered to be serious, while all other Grade 4 TEAEs were serious.

Overall, 23 participants (52.3%) reported a **Grade ≥ 3 treatment-related TEAE**; 6 participants (13.6%) reported a Grade 4 treatment-related TEAE, and 1 participant (2.3%) reported a Grade 5 or fatal treatment-related TEAE. Grade 4 treatment-related TEAEs were myocardial ischemia, vascular graft occlusion, transaminases increased, WBC count decreased, cerebrovascular accident, embolism, and thrombosis, each reported in 1 participant. Of these, transaminases increased and WBC count decreased were not considered to be serious. Fatal TEAEs are described below.

Assessor's comment:

In Study AP24534-11-001, the most commonly reported TEAEs were within the SOCs haematological and gastrointestinal disorders and infections. Overall, the AE profile was what may be expected from treatment with ponatinib in combination with chemotherapy.

Febrile neutropenia and pneumonia were very commonly reported (in 65.5% and 34.5% of patients, respectively), in Study AP24534-11-001. In the SmPC section 4.8, these reactions are reported as Common (i.e. 1-10%). Further, urinary tract infection was very commonly reported but is not previously listed as ADR. In Study AP24534-11-001, these reactions were apparently not, in most of the cases, considered treatment-related by the investigator. No updates to the ADR table or description of selected adverse reactions in the SmPC are proposed but the MAH introduced warnings that the frequency of some ADRs, including VTEs may be increased when ponatinib is used in combination with chemotherapy.

Febrile neutropenia, pneumonia and urinary tract infection were not as commonly reported in Study INCB 84344-201, where the patients did not receive concomitant chemotherapy, as in Study AP24534-11-001.

3.5.4. Serious adverse event/deaths/other significant events

3.5.4.1. Deaths

Study AP24534-11-001 – Ponatinib + hyper CVAD

Death was reported in altogether 20 participants (23.0%; see Table 32): 5 participants died due to complications from post-autologous stem cell transplants, 6 participants due to post-relapse/lung CA, 4 participants due to cardiac events (2 events were TEAEs), 4 participants due to multiple organ failure/sepsis (3 events were TEAEs), and 1 participant due to a TEAE of intracranial haemorrhage.

Five participants (5.6%) died during the study or follow-up period with Grade 5 TEAEs (Table 40). An additional death occurred more than 30 days after the participant's last dose, but the event was reported as Grade 5 while the participant was in the study period. The death was considered a non-study event. Thus, altogether six treatment-emergent AEs leading to death are listed in Table 40.

Two of the six deaths (unspecified cause; 'Death') were considered to be possibly treatment-related. In both cases, the participants died at home and no autopsies were performed.

- One case involved a 34-year-old male, who was a smoker, with a history of pulmonary embolism and DVT, and who had recently been in the hospital for MI. Two days after discharge, he died at home. The cause of death was not provided, although extension and/or complications of MI, vasospasm, arrhythmia, and pulmonary embolism were thought to be possibilities. Although ponatinib has been associated with arterial thrombosis and myocardial infarction, the role of ponatinib in this case of sudden death is unclear. Investigator and sponsor assessed the event of death as possibly related.
- The second case was a 60-year-old female with ALL who was reported to have died at home in her sleep. The participant had recently been admitted to the hospital after receiving Cycle 4, Day 20 of hyper-CVAD plus ponatinib, and at that time was treated for pneumonia, pleural effusions, and pericarditis. She was discharged approximately 3 weeks after hospital admission. The investigator assessed the death as possibly related to ponatinib; however, the cause of death was not specified. The patient had recently been admitted to the hospital after receiving cycle 4, day 20 of hyper CVAD plus ponatinib, and was treated at that time for pneumonia, pleural effusions, and pericarditis. She was discharged approximately 3 weeks before death, and ponatinib was put on hold due to pleural effusions. The investigator assessed the death as possibly related to ponatinib, and the sponsor could not rule out a causal association.

Table 40. AP24534 -11-001: TEAEs Leading to Death by SOC and PT (Enrolled Population)

MedDRA SOC MedDRA PT	Hyper-CVAD + Ponatinib N = 87 n (%)
Subjects with any TEAE leading to death	6 (6.9)[a]
General disorders and administration site conditions	2 (2.3)
Death[a]	2 (2.3)
Infections and infestations	2 (2.3)
Sepsis	2 (2.3)
Cardiac disorders	1 (1.1)
MI[a,b]	1 (1.1)
Gastrointestinal disorders	1 (1.1)
Colitis	1 (1.1)
Immune system disorders	1 (1.1)
Immune system disorders – Other	1 (1.1)
Nervous system disorders	1 (1.1)
Haemorrhage intracranial	1 (1.1)

AE = adverse event; CSR = clinical study report; hyper-CVAD = hyper-fractionated cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone; MedDRA = Medical Dictionary for Regulatory Activities; MI = myocardial infarction; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Note: MedDRA Dictionary (v23.0) was used for coding AEs.
Note: Subjects with one or more AEs within a level of MedDRA term is counted only once in that level.
Note: TEAE is defined as any AE that occurs after administration of the first dose of any study drug and through 30 days after the last dose of any study drug.
Note: Data cutoff date of 14 DEC 2020.
[a] One participant death (MI and death) occurred more than 30 days after the participant's last dose, but the event was reported as Grade 5 while the participant was in the study period. The death was considered a nonstudy event. Therefore, it has been reported as a sixth death in some tables.
[b] Nonserious.

Study INCB 84344-201 – patients aged ≥ 60 years or ineligible for chemotherapy and SCT

A total of 22 participants (50.0%) were reported to have died at the time of 30 Sept 2021 DCO. The reported causes of death were disease progression (ALL) in 9 participants (20.5%), other (not due to toxicity or relapse) in 6 participants (13.6%), cardiovascular disease in 2 participants (4.5%), toxicity in 2 participants (4.5%), unknown in 2 participants (4.5%), and both disease progression (ALL) and severe sepsis (reported as unrelated to ponatinib) in 1 participant (2.3%)

For 5 participants (11.4%) death was reported as a Grade 5 TEAE (Table 41).

One of the fatal TEAEs was considered by the investigator to be possibly related to ponatinib. The event was reported as sudden death on Day 671. The participant's medical history included impaired fasting blood glucose, arterial hypertension, prostatic hypertrophy, prostate cancer, hyperuricemia, Grade 1 hypertriglyceridemia, Grade 2 anaemia, Grade 3 neutropenia, and Grade 3 thrombocytopenia. All investigations including ECGs and ECHOs performed at baseline and during the study period were normal, except for an ECG performed on Day 125.

The fatal TEAEs of septic shock (1 participant), pneumonia (2 participants), and bronchopulmonary aspergillosis and respiratory failure (1 participant) were not considered by the investigator to be related to ponatinib treatment. Among them, 2 fatal TEAEs that occurred early in the study were pneumonia reported on Day 21 and pneumonia with Grade 3 febrile neutropenia reported on Day 34. Pneumonia was reported in the medical history of both participants. The other 2 fatal TEAEs were a

case of respiratory failure and pulmonary aspergillosis reported on Day 402 and septic shock reported on Day 875. These participants had a medical history of hypertension (4 participants), anaemia (3 participants), leukopenia (3 participants), and thrombocytopenia (3 participants).

Table 41. INCB 84344-201: TEAEs With a Fatal Outcome by SOC and PT (Full Analysis Set)

MedDRA SOC **MedDRA PT**	**Total** **N = 44** **n (%)**
General disorders and administration site conditions	1 (2.3)
Sudden death	1 (2.3)
Infections and infestations	4 (9.1)
Bronchopulmonary aspergillosis	1 (2.3)
Pneumonia	2 (4.5)
Septic shock	1 (2.3)
Respiratory, thoracic, and mediastinal disorders	1 (2.3)
Respiratory failure	1 (2.3)

AE = adverse event; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Note: TEAEs are any AE either reported for the first time or worsening of a pre-existing event after first administration of study drug and within 30 days of the last dose of study drug.
Note: Participants were counted once under each PT.
Note: AEs were coded using MedDRA 22.0.
Note: Data cutoff date of 30 SEP 2021.

Assessor's comment:

Overall, in the two studies, 11 Grade 5 TEAEs were reported within the two studies. Of these, three were suggested as probably or possibly treatment-related by the investigator. Two of the three treatment-related events occurred in Study AP24534-11-001, i.e. ponatinib in combination with chemotherapy, and one in Study INCB 84344-201. The cause of death was unspecified in all three cases that were assessed as possibly treatment related ('death' or 'sudden death').

One patient in Study AP24534-11-001 had a medical history of pulmonary embolism and had recently been treated in hospital for myocardial infarction. The second patient in Study AP24534-11-001 had recently been hospitalized and treated for pneumonia, pleural effusions, and pericarditis.

In the third case, in Study INCB 84344-201 (69 year-old male, 'sudden death'), the patient's medical history included impaired fasting blood glucose, arterial hypertension, prostatic hypertrophy, prostate cancer, hyperuricemia, Grade 1 hypertriglyceridemia, Grade 2 anaemia, Grade 3 neutropenia, and Grade 3 thrombocytopenia, however, ECGs and ECHOs performed during the study had been normal.

A causality assessment is difficult to make based on the available information on the deaths that were considered treatment-related. The cases seem confounded by medical history of the patients.

The 4 fatal cases in Study AP24534-11-001 that were *not* considered treatment-related included the PT:s sepsis (2 patients), colitis, immune system disorders – other (hemophagocytic lymphohistiocytosis; HLH), and intracranial haemorrhage (Table 40). In the cases of sepsis and colitis, the investigator (and sponsor) considered the events possibly related to the underlying ALL. The intracranial haemorrhage was due to a fall. The HLH case was confounded by immunodeficiency due to underlying disease and concomitant medications.

In Study INCB 84344-201, there were three fatal TEAEs due to infections, which were not considered treatment-related. Infectious treatment-emergent deaths were reported also in the PACE trial and were, also then, in most cases not considered treatment-related.

Overall, the pattern of deaths due to TEAEs in Study AP24534-11-001 and Study INCB 84344-201 do not give raise to new concerns compared with previously available safety data for ponatinib. However, the small study size may preclude definite conclusions.

3.5.4.2. Serious adverse events

Study AP24534-11-001 - Ponatinib + hyper CVAD

A total of 79 participants (90.8%) had at least 1 serious TEAE, including 77 participants (88.5%) with at least 1 that was Grade ≥ 3 in severity. The exposure-adjusted rate per 100 person-years was 2.86 (95% CI: 1.23, 4.49) with a total person-years of 27.64. Of note, the number of serious TEAEs includes fatal TEAEs (listed in Table 40).

The most common serious TEAE by SOC (reported in ≥ 10% of participants) were Lymphatic system disorders (51 participants, 58.6%), Infections and infestations (48 participants, 55.2%), General disorders and administration site conditions (34 participants, 39.1%), Gastrointestinal disorders (30 participants, 34.5%), Nervous system disorders (17 participants, 19.5%), Vascular disorders (13 participants, 14.9%), and Cardiac disorders (11 participants, 12.6%).

The most frequently (≥ 15 participants) reported serious TEAEs by PT were febrile neutropenia, pyrexia, and pneumonia (see Table 42).

Table 42. AP24534 -11-001: Serious TEAEs Reported in > 5% of Participants by PT

MedDRA PT	Hyper-CVAD + Ponatinib N = 87 n (%)
Febrile neutropenia	48 (55.2)
Pyrexia	30 (34.5)
Pneumonia	20 (23.0)
Sepsis	14 (16.1)
Urinary tract infection	11 (12.6)
Abdominal pain	10 (11.5)
Infections and infestations – Other	8 (9.2)
Headache	7 (8.0)
Atrial fibrillation	6 (6.9)
Colitis	6 (6.9)
Embolism	6 (6.9)
Skin infection	6 (6.9)
Back pain	5 (5.7)
Hypotension	5 (5.7)
Nausea	5 (5.7)
Noncardiac chest pain	5 (5.7)

AE = adverse event; CSR = clinical study report; hyper-CVAD = hyper-fractionated cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event.
Note: A TEAE is defined as any AE that occurs after administration of the first dose of any study drug and through 30 days after the last dose of any study drug.
Note: MedDRA v23.0 was used for coding AEs.
Note: Participants with 1 or more AEs within a level of MedDRA term are counted only once in that level.
Note: Data cutoff date of 14 DEC 2020.

Treatment-related serious TEAEs

The serious TEAEs in Study AP24534-11-001 were considered treatment-related (to ponatinib and/or chemotherapy) in 39 patients (44.8%), including 32 (36.8%) with at least one that was Grade ≥ 3 in severity (Table 43). The following treatment-related Grade 4 serious TEAEs were reported: lipase increased (2 participants) and gastrointestinal disorders – other (small ischemic bowel obstruction pneumatosis, 1 participant). A Grade 5 serious treatment-related TEAE occurred in 2 participants ('death'; see above).

Table 43. AP24534 -11-001: Treatment-Related Serious TEAEs Reported in > 1 Participant by PT (Enrolled Population)

MedDRA PT	Hyper-CVAD + Ponatinib N = 87 n (%)
Febrile neutropenia	6 (6.9)
Embolism	4 (4.6)
Nausea	4 (4.6)
Atrial fibrillation	3 (3.4)
Pancreatitis	3 (3.4)
Pyrexia	3 (3.4)
Death[a]	2 (2.3)
Hypertension	2 (2.3)
Ileus	2 (2.3)
Lipase increased	2 (2.3)
Pancreas infection	2 (2.3)
Stomatitis	2 (2.3)

AE = adverse event; CSR = clinical study report; hyper-CVAD = hyper-fractionated cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone; MedDRA = Medical Dictionary for Regulatory Activities; MI = myocardial infarction; PT = preferred term; TEAE = treatment-emergent adverse event.

Note: A TEAE is defined as any AE that occurs after administration of the first dose of any study drug and through 30 days after the last dose of any study drug. MedDRA v23.0 was used for coding AEs. Participants with 1 or more AEs within a level of MedDRA term are counted only once in that level.

Note: Data cutoff date of 14 DEC 2020.

[a] One participant death (MI and death) occurred more than 30 days after the participant's last dose, but the event was reported as Grade 5 while the participant was in the study period. The death was considered a non-study event. Therefore, it has been reported as a sixth death in some tables.

Study INCB 84344-201 - patients aged ≥ 60 years or ineligible for chemotherapy and SCT

As of the DCO date of 30 SEP 2021, a total of 23 participants (52.3%) had a serious TEAE. This number of serious TEAEs includes fatal TEAEs (previously described in Table 41).

Serious TEAEs by SOC reported in > 2 participants were Cardiac disorders, Infections and infestations, and Vascular disorders (each 7 participants; 15.9%); and Nervous system disorders and General disorders and administration site conditions (each 3 participants; 6.8%).

Serious TEAEs by PT reported in ≥ 2 participants were acute coronary syndrome, arterial occlusive disease, atrial fibrillation, cardiac failure, and pneumonia (Table 44).

Overall, 11 participants (25.0%) reported a Grade 3 serious TEAE, 7 participants (15.9%) reported a Grade 4 serious TEAE, and 5 participants (11.4%) reported a Grade 5 or fatal serious TEAE. The following Grade 4 serious TEAEs were each reported in 1 participant: myocardial ischemia, multiple organ dysfunction syndrome, enterococcal sepsis, escherichia sepsis, staphylococcal sepsis, ALT increased, vascular graft occlusion, neoplasms benign, malignant, and unspecified (including cysts and polyps), lung adenocarcinoma, cerebrovascular accident, acute kidney injury, and embolism. Grade 5 SAEs were bronchopulmonary aspergillosis and respiratory failure (both events in 1 participant), pneumonia (2 participants), septic shock (1 participant), and sudden death (1 participant; see above)

The outcome for the majority of non-fatal serious TEAEs was recovered/resolved or recovering/resolving.

Table 44. INCB 84344-201: Serious TEAEs by PT (Full Analysis Set)

MedDRA PT	Total N = 44 n (%)
Acute coronary syndrome	3 (6.8)
Arterial occlusive disease	2 (4.5)
Atrial fibrillation	2 (4.5)
Cardiac failure	2 (4.5)
Pneumonia	2 (4.5)
Acute kidney injury	1 (2.3)
ALT increased	1 (2.3)
Arterial stenosis	1 (2.3)
AST increased	1 (2.3)
Asthenia	1 (2.3)
Bronchopulmonary aspergillosis	1 (2.3)
Carotid artery stenosis	1 (2.3)
Cerebrovascular accident	1 (2.3)
Colitis ischaemic	1 (2.3)
Deep vein thrombosis	1 (2.3)
Embolism	1 (2.3)
Enterococcal sepsis	1 (2.3)
Erythema	1 (2.3)
Escherichia sepsis	1 (2.3)
Gastrointestinal disorder	1 (2.3)
Haemorrhage	1 (2.3)
Legionella infection	1 (2.3)
Leukopenia	1 (2.3)
Lung adenocarcinoma	1 (2.3)
Lung disorder	1 (2.3)
Multiple organ dysfunction syndrome	1 (2.3)
Myocardial ischaemia	1 (2.3)
Pancreatitis	1 (2.3)
Pericardial effusion	1 (2.3)
Peripheral arterial occlusive disease	1 (2.3)
Peripheral ischaemia	1 (2.3)
Rash	1 (2.3)
Respiratory failure	1 (2.3)
Septic shock	1 (2.3)
Staphylococcal infection	1 (2.3)

MedDRA PT	Total N = 44 n (%)
Staphylococcal sepsis	1 (2.3)
Sudden death	1 (2.3)
Transient ischaemic attack	1 (2.3)
Transitional cell carcinoma	1 (2.3)
Urosepsis	1 (2.3)
Vascular graft occlusion	1 (2.3)

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event.
Note: TEAEs are any AE either reported for the first time or worsening of a pre-existing event after first administration of study drug and within 30 days of the last dose of study drug.
Note: Participants were counted once under each PT.
Note: AEs were coded using MedDRA v22.0.
Note: Data cutoff date of 30 SEP 2021.

Treatment-related serious TEAEs

In Study INCB 84344-201, a total of 14 participants (31.8%) had at least 1 treatment-related serious TEAE (Table 45). Events by SOC reported in ≥ 2 participants were Cardiac disorders (5 participants, 11.4%), Vascular disorders (5 participants, 11.4%), and General disorders and administration site conditions, Nervous system disorders, and Skin and subcutaneous disorders (each 2 participants, 4.5%). The most frequently reported treatment-related serious TEAE by PT was acute coronary syndrome, reported in 3 participants. All other treatment-related serious TEAEs were each reported in 1 participant. The following treatment-related Grade 4 serious TEAEs were each reported in 1 participant: myocardial ischemia, vascular graft occlusion, cerebrovascular accident, and embolism. A Grade 5 serious treatment-related TEAE occurred in 1 participant (sudden death; see above). The remaining serious TEAEs were Grade 3.

Table 45. INCB 84344-201: Treatment-Related Serious TEAEs by PT (Full Analysis Set)

MedDRA PT	Total N = 44 n (%)
Acute coronary syndrome	3 (6.8)
Arterial occlusive disease	2 (4.5)
Asthenia	1 (2.3)
Atrial fibrillation	1 (2.3)
Cardiac failure	1 (2.3)
Carotid artery stenosis	1 (2.3)
Cerebrovascular accident	1 (2.3)
Deep vein thrombosis	1 (2.3)
Embolism	1 (2.3)
Erythema	1 (2.3)
Leukopenia	1 (2.3)

MedDRA PT	Total N = 44 n (%)
Lung disorder	1 (2.3)
Myocardial ischaemia	1 (2.3)
Pancreatitis	1 (2.3)
Peripheral arterial occlusive disease	1 (2.3)
Peripheral ischaemia	1 (2.3)
Rash	1 (2.3)
Sudden death	1 (2.3)
Vascular graft occlusion	1 (2.3)

AE = adverse event; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event.
Note: TEAEs are any AE either reported for the first time or worsening of a pre-existing event after first administration of study drug and within 30 days of the last dose of study drug.
Note: Treatment-related TEAEs are TEAEs judged as related to ponatinib by the investigator or with a missing causality. Participants were counted once under each PT. AEs were coded using MedDRA 22.0.
Note: Data cutoff date of 30 SEP 2021.

Assessor's comment:

In the previous PACE trial (ponatinib monotherapy), at the initial report with a median duration of ponatinib therapy of 120 days in the BP-CML/Ph+ ALL population, serious AEs were reported in 81% of the BP-CML/Ph+ ALL population. The most common treatment-emergent SAEs in the BP-CML/Ph+ ALL population were febrile neutropenia (12.1%); pneumonia (9.3%) and sepsis (5.6%). In **Study AP24534-11-001**, serious TEAEs were reported in 91% of patients. The most commonly reported events were the same as in the PACE trial, but the rates were considerably higher, which could be explained by the treatment with chemotherapy as well as the longer treatment duration (median 398 days).

Six patients in Study AP24534-11-001 (6.9%) had a serious TEAE of embolism, of which four (4.6%) were considered treatment-related by the investigator (see also section 5.5.4.3 below). Four of these patients had a Grade 3 event (of which three were considered treatment-related), the remaining two were Grade 2. One patient had a dose interruption, in the other five serious cases the event did not lead to any change in the treatment.

In **Study INCB 84344-201**, about half of the patients (52%) experienced a SAE. SAEs were most commonly reported within the SOCs Cardiac disorders, Infections and infestations, and Vascular disorders. The most commonly reported PTs (reported in ≥ 2 patients) were acute coronary syndrome, arterial occlusive disease, atrial fibrillation, cardiac failure, and pneumonia. The most frequently reported *treatment-related* SAEs by PT was acute coronary syndrome, reported in 3 participants. As further described below, SAEs leading to treatment discontinuation in Study INCB 84344-201 included cardiac and vascular disorders and infections, where the cardiac and vascular disorders were generally assessed as treatment-related, while infections were not.

3.5.4.3. Adverse events of special interest – vascular occlusive events

Vascular occlusive events (VOEs), including arterial occlusive events (AOEs) and venous thromboembolic events (VTEs), have been identified as AESIs for ponatinib.

In the PACE trial, which was the basis for the original approval of Iclusig, arterial cardiovascular, cerebrovascular, and peripheral vascular occlusive adverse reactions (treatment-emergent frequencies) occurred in 13%, 9%, and 11% of ponatinib-treated patients, respectively. Overall AOEs occurred in 25% of ponatinib-treated patients from the PACE trial with a minimum of 64 months follow-up, with serious adverse reactions occurring in 20% of patients. Some patients experienced more than one type of event. VTEs (treatment-emergent frequencies) occurred in 6% of patients. In this trial, the incidence of thromboembolic events was higher in patients with Ph+ ALL or blast phase-CML than those with accelerated phase-CML or chronic phase-CML. No venous occlusive events were fatal in the PACE trial.

Study AP24534-11-001 - Ponatinib + hyper CVAD

Overall, **treatment-emergent AOEs (TE-AOEs)** occurred in 12 participants (13.8%), of which 8 (9.2%) had TE-AOEs that were related to treatment, and 3 (3.4%) had treatment-related TE-AOEs that were Grade ≥ 3.

The median number of days to when the first TE-AOE was observed was approximately 56 days (range: 11-45 days). The exposure-adjusted rate per 100 person-years for TE-AOEs was 7.89 (95% CI: 3.16, 12.63) with a total person-years of 152.00.

The most common TE-AOEs by PT (≥ 2 participants) were angina pectoris and MI (Table 46). Of the 8 participants with TE-AOEs related to treatment, the most common TE-AOEs by PT were angina pectoris (4 participants, 4.6%), followed by MI (3 participants, 3.4%) and acute coronary syndrome and transient ischemic attack (1 participant, 1.1% each).

Serious TE-AOEs occurred in 5 participants (5.7%), 4 participants (4.6%) had serious TE-AOEs that were reported as treatment-related, and 1 participant (1.1%) had serious treatment-related TE-AOEs that were Grade ≥ 3.

Two dose interruptions for MI and embolism occurred before the protocol amendment implementing the mandatory ponatinib dose reductions.

Grade 3 or 4 AOEs occurred in 4 participants (angina pectoris, 1 participant; and MI, 3 participants) and a Grade 5 AOE occurred in 1 participant (MI).

Table 46. AP24534 -11-001: TE-AOEs by SOC and PT (Enrolled Population)

MedDRA SOC **MedDRA PT**	**Hyper-CVAD + Ponatinib** **N = 87** **n (%)**
Cardiac disorders	11 (12.6)
Angina pectoris	7 (8.0)
MI	4 (4.6)
Acute coronary syndrome	1 (1.1)
Blood and lymphatic system disorders	1 (1.1)
Disseminated intravascular coagulation	1 (1.1)
Nervous system disorders	1 (1.1)
Transient ischaemic attack	1 (1.1)

AE = adverse event; CSR = clinical study report; hyper-CVAD = hyper-fractionated cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone; MedDRA = Medical Dictionary for

Regulatory Activities; MI = myocardial infarction; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event; TE-AOE = treatment-emergent arterial occlusive event.
Note: A TEAE is defined as any AE that occurs after administration of the first dose of any study drug and through 30 days after the last dose of any study drug. MedDRA v23.0 was used for coding AEs. Participants with 1 or more AEs within a level of MedDRA term are counted only once in that level.
Note: Data cutoff date of 14 DEC 2020.

Overall, **treatment-emergent VTEs** (TE-VTEs) occurred in 11 participants (12.6%), of which 8 (9.2%) had a VTE that was considered related to treatment and two (2.3%) had treatment-related TE-VTEs that were Grade ≥ 3 (Table 47).

The median number of days to when the first TE-VTE was observed in participants was approximately 79 days. The exposure-adjusted rate per 100 person-years for TE-VTEs was 7.63 (95% CI: 2.71, 12.655) with a total person-years of 144.21.

The only TE-VTEs by PT were embolism (10 participants, 11.5%) and thrombophlebitis superficial 1 participant, 1.1%).

Under the PT of embolism, the reported terms were deep vein thrombosis (7 participants), embolism (3 participants) pulmonary embolism (2 participants), renal vein thrombosis (1 participant), and both deep vein thrombosis and pulmonary embolism (1 participant).

The single event of thrombophlebitis superficial was considered **treatment-related** and there were 7 participants (8.0%) with **treatment-related TE-VTEs of embolism**. Study-drug-related TE-VTEs under the PT of embolism were deep vein thrombosis (5 participants), embolism (3 participants), and pulmonary embolism (1 participant), and renal vein thrombosis (1 participant).

Serious TE-VTEs occurred in 6 participants (6.9%); 4 participants (4.6%) had serious TE-VTEs that were reported as treatment-related.

Grade 3 or 4 VTEs occurred in 4 participants with embolism. No subjects had Grade 5 VTEs.

Table 47. AP24534 -11-001: TE-VTEs (Enrolled Population)

Variables	Hyper-CVAD + Ponatinib N = 87 n (%)
TE-VTEs, n (%)	11 (12.6)
Treatment-Related	8 (9.2)
Grade 3-5	4 (4.6)
Grade 3-5 Treatment-Related	2 (2.3)
Serious TE-VTEs, n (%)	6 (6.9)
Treatment-Related	4 (4.6)
Grade 3-5	4 (4.6)
Grade 3-5 Treatment-Related	2 (2.3)
Days on study when first TE-VTE observed	
N	11
Mean (STD)	219.9 (425.38)
Median	79.0
Q1, Q3	28.0, 111.0
Min, max	1, 1451
Dose intensity during last 30 days prior to first occurred TE-VTE (mg/day)	
N	11
Mean (STD)	26.0 (14.20)
Median	22.3
Q1, Q3	14.5, 40.0
Min, max	4, 45

AE = adverse event; CSR = clinical study report; hyper-CVAD = hyper-fractionated cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and dexamethasone; max = maximum; MedDRA = Medical Dictionary for Regulatory Activities; min = minimum; Q = quartile; STD = standard deviation; TEAE = treatment-emergent adverse event; TE-VTE = treatment-emergent venous thromboembolic event.

Note: TEAE is defined as any AE that occurs after administration of the first dose of any study drug and through 30 days after the last dose of any study drug. MedDRA Dictionary (v23.0) was used for coding AEs. Participants with one or more AEs within a level of MedDRA term are counted only once in that level.

Note: Data cutoff date of 14 DEC 2020.

Study INCB 84344-201 - patients aged ≥ 60 years or ineligible for chemotherapy and SCT

As of the DCO date of 30 SEP 2021, 15 participants (34.1%) had a TE-VOE.

Events in the Cardiac disorders and General disorders and administration site conditions SOCs were most common (11.4% each), and the most frequently reported PTs (≥ 2 participants) were chest pain, acute coronary syndrome, arterial occlusive disease, and embolism (Table 48).

Ten participants had 15 TE-VOEs **related to treatment**, and the most common (≥ 2 participants) treatment-related TE-VOEs by PT were acute coronary syndrome, arterial occlusive disease, and embolism.

Overall, Grade 3 TE-VOEs were reported in 5 participants (11.4%) and Grade 4 TE-VOEs were reported in 4 participants (9.1%). The following Grade 3 TE-VOEs were reported: acute coronary syndrome (3 participants, 6.8%), arterial occlusive disease (2 participants, 4.5%), and carotid artery stenosis, peripheral ischemia, and peripheral arterial occlusive disease (1 participant each, 2.3% each). The following Grade 4 TE-VOEs were each reported in 1 participant (2.3%): myocardial ischemia, vascular graft occlusion, cerebrovascular accident, and embolism. There were no fatal TE-VOEs during the study reporting period; 1 fatal TE-VOE (acute coronary syndrome) occurred more than 30 days after the participant discontinued ponatinib.

The following TE-VOEs were serious: acute coronary syndrome (3 participants), arterial occlusive disease (2 participants), and vascular graft occlusion, carotid artery stenosis, peripheral arterial occlusive disease, cerebrovascular accident, embolism, transient ischemic attack, peripheral ischemia, myocardial ischemia, myocardial infarction, and thrombosis (1 participant each). All serious TE-VOEs, except for the transient ischemic attack and myocardial infarction, were considered by the investigator to be related to ponatinib.

Table 48. INCB 84344-201: TE-VOEs by SOC and PT (Full Analysis Set)

MedDRA SOC MedDRA PT	Total N = 44 n (%)
Cardiac disorders	5 (11.4)
Acute coronary syndrome	3 (6.8)
Angina pectoris	1 (2.3)
Myocardial ischaemia	1 (2.3)
General disorders and administration site conditions	5 (11.4)
Chest pain	5 (11.4)
Injury, poisoning, and procedural complications	1 (2.3)
Vascular graft occlusion	1 (2.3)
Nervous system disorders	4 (9.1)
Carotid arteriosclerosis	1 (2.3)
Carotid artery stenosis	1 (2.3)
Cerebrovascular accident	1 (2.3)
Transient ischaemic attack	1 (2.3)
Vascular disorders	5 (11.4)
Arterial occlusive disease	2 (4.5)
Embolism	2 (4.5)
Peripheral arterial occlusive disease	1 (2.3)
Peripheral ischaemia	1 (2.3)

AE = adverse event; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event; TE-VOE = treatment-emergent vascular occlusive events.

Note: TEAEs are any AE either reported for the first time or worsening of a pre-existing event after first administration of study drug and within 30 days of the last dose of study drug. Participants were counted once under each PT. AEs were coded using MedDRA v22.0.

Note: Data cutoff date of 30 SEP 2021.

MAH's Discussion

In Study AP24534-11-001, TE-AOEs occurred in 12 participants (13.8%), and TE-VTEs occurred in 11 participants (12.6%), with a median number of days to first TE-AOE and TE-VTE at approximately 56 and 79 days, respectively. When incidence rates were adjusted for exposure, the incidences of TE-AOEs (7.89 per 100 person-years) and TE-VTEs (7.63 per 100 person-years) were similar. Study-drug-related TE-AOEs and TE-VTEs occurred in 9.2% of participants each. Grade ≥ 3 TE-AOEs and TE-VTEs occurred in 4.6% of participants each. Serious TE-AOEs and TE-VTEs occurred in 5.7% and 6.9% of participants, respectively.

In Study INCB 84344-201, TE-VOEs occurred in 15 participants (34.1%), and 10 participants had 15 TE-VOEs that were treatment-related. Grade 3 TE-VOEs were reported in 5 participants (11.4%), and Grade 4 TE-VOEs were reported in 4 participants (9.1%).

The duration of ponatinib treatment for Ph+ ALL in Studies AP24534-11-001 and INCB 84344-201 is longer than when used in later lines of therapy and thus there are no direct comparisons from other studies of the frequency of VOEs with long-term treatment. However, some comparisons can be made with long-term ponatinib treatment in Study AP24534-10-201 (PACE), which enrolled participants with refractory CML and Ph+ ALL. In this study, median overall exposure was 508 days (range 1-2223 days) and the median dose intensity was 30.7 mg/day. It is medically valid to separate arterial and venous events, and, considering the possible differences in arterial vasculature, to further separate arterial events into cardiac, cerebral, and peripheral vascular events. Treatment-emergent VOEs were reported in 128 of 449 participants (28.5%), most of which were TE-AOEs (111 participants; 24.7%) versus TE-VTEs (27 participants; 6.0%). By disease group, a higher proportion of participants in the CP-CML disease group (92/270 participants; 34.1%) were reported to have TE-VOEs compared with the much smaller Ph+ ALL disease group (6/32 participants; 18.8%), with a similar trend in the proportions of participants having serious TE-VOEs. Median duration of exposure was higher in the CP-CML group (978.5 days, range 3-2223 days) compared with the BP-CML/Ph+ ALL group (85.5 days, range 1-1798 days).

When the incidence of TE-AOEs per unit exposure was taken into account, the rate of TE-AOEs per 100 patient years in Study AP24534-10-201 (PACE) was 14.09 at 46 months and 13.82 at 53 months, and the overall rate of TE-VTEs per 100 patient-years was 2.75.

Assessor's comment:

In the PACE trial, which was the basis for the original approval of Iclusig, overall AOEs occurred in 25% of ponatinib-treated patients with a minimum of 64 months follow-up, with serious adverse reactions occurring in 20% of patients. Some patients experienced more than one type of event. Adjusted for exposure, the rate of TE-AOEs in the PACE trial was 13.8 per 100 Patient years at 53 months.

In the PACE trial, VTEs (treatment-emergent frequencies) occurred in 6% of patients. In this trial, the incidence of thromboembolic events was higher in patients with Ph+ ALL or blast phase (BP)-CML than those with accelerated phase (AP)-CML or chronic phase (CP)-CML. No venous occlusive events were fatal in the PACE trial. Adjusted for exposure, the rate of TE-VTEs in the PACE trial was 2.75 per 100 Patient years.

In **Study AP24534-11-001**, overall AOEs occurred in 13.8% of patients. These events were considered treatment-related (by the investigator) in 9.2% of patients, and 3.4% had events of Grade ≥ 3. The most common treatment-emergent AOEs by PT were angina pectoris (4.6%), followed by MI (3.4%) and acute coronary syndrome and transient ischaemic attack (1.1% each). Adjusted for exposure, the incidence of AOEs was 7.9 per 100 patient years. Thus, the incidence seems to be lower than in the PACE trial. Contrary to the PACE trial, dose reductions to 30 mg after Day 14 in Cycle 1, and to 15 mg once CMR was achieved, were introduced in Study AP24534-11-001, in line with the current recommendations in the SmPC, in order to minimise the risk for AOEs. VTEs occurred in 12.6% of patients, or at an incidence of 7.6 per 100 patient years, which is a higher rate than in the PACE trial, considering also that the PACE study included mostly patients with accelerated and chronic phase CML, who were reported to have a higher rate of VTEs than patients with BP-CML or Ph+ALL. However, exposure-adjusted rates were not compared between the different disease groups in PACE, and the observed difference might be due to a longer median duration of exposure in AP-CML and CP-CML. VTEs are reported ADRs also for e.g. MTX and Cyclophosphamide, and an increased risk at combination of ponatinib with chemotherapy must be taken into consideration and is described in the SmPC. Nevertheless, the serious VTE events reported in Study AP24534-11-001 appear to have been manageable as they did not lead to treatment discontinuation, and only in one case to treatment interruption.

In Study INCB 84344-201, VOEs were reported in a total of 15 patients (34.1% of patients). The MAH did not report rates for AOEs and VTEs separately from this trial. Acute coronary syndrome was reported in 3 participants, arterial occlusive disease and embolism in 2 participants. Some patients had more than one reported event. There were 15 serious events in 9 patients of which 13 were considered related to treatment. In three cases ponatinib was withdrawn, and in two cases the event led to dose interruption. In the remaining cases the event did not lead to a change in treatment. The MAH did not present exposure-adjusted rates for Study INCB 84344-201. Considering the shorter median duration of treatment in Study INCB 84344-201 (415 days) than in the PACE study (508 days), the VOE event rate appears to be higher in Study INCB 84344-201 than in the PACE trial, where TE-VOEs were reported in 28.8% of the participants. However, in the PACE trial, the rate of VOEs was lower in Ph+ALL patients (6/38 patients; 18.8%) than in the overall population. The median duration of treatment in Ph+ALL patients in PACE was considerably lower than in Study INCB 84344-201 (median 85 days). The average daily dose was fairly similar between the two trials. Thus, overall, exposure-adjusted rate of VOEs may not be higher in Study INCB 84344-201 than in PACE. Definite conclusions are, however, difficult to draw due to limited number of patients in Study INCB 84344-201.

In Study INCB 84344-201, there were no recommendation to reduce the dose to 15 mg at CMR, however, such a recommendation has been introduced in the SmPC, which might possibly affect the rate of VOEs in the indicated population, but this cannot be concluded from the available data.

3.5.5. Laboratory findings

Study AP24534-11-001 - Ponatinib + hyper CVAD

Overall, median AST, ALT, and triacylglycerol lipase were in normal ranges from baseline to 36 months. Postbaseline (defined as the most exceeded record for each participant for each parameter up to 93 months), there was a higher percentage of shifts from normal to high in ALT and AST than triacylglycerol lipase (48.3%, 49.4%, and 21.8%, respectively.

Study INCB 84344-201 - patients aged ≥ 60 years or ineligible for chemotherapy and SCT

As of the DCO date of 30 SEP 2021, mean values for lactate dehydrogenase decreased from baseline and during the study and ALT and GGT variably showed some increases and decreases from baseline. Some of these results were outside the normal range (high) for some participants. The mean values for other clinical chemistry results did not change notably during the study, and the results were generally within the normal range for most participants.

During the study, there were decreases from baseline in the mean values for blasts/leukocytes and lymphocytes/leukocytes and increases from baseline in the mean values for haemoglobin, neutrophils/leukocytes, and platelets. The mean values for leukocytes initially decreased during the study and then variably showed increases and decreases from baseline.

3.5.6. Safety in special populations

No new information provided.

Of the 87 participants enrolled in Study AP24534-11-001, only 15 participants (17.2%) were ≥ 65 years of age. Of the 44 participants enrolled in Study INCB 84344-201, 18 participants (40.9%) were ≤ 65 years of age and 26 participants were 65 years of age or older. Small numbers of participants preclude definitive conclusions on potential differences in safety profile due to age.

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

The potential for pharmacokinetic drug interactions at use according to the currently proposed indication are discussed in the Clinical pharmacology section above.

The previously approved SmPC informs that ponatinib as an inhibitor of renal transport proteins might cause increased concentrations of renally eliminated drugs such as MTX.

3.5.8. Discontinuation due to adverse events

Study AP24534-11-001 - Ponatinib + hyper CVAD

A total of 20 participants (23.0%) experienced a serious TEAE leading to treatment discontinuation. All TEAEs leading to treatment discontinuation were serious. Serious TEAEs leading to treatment discontinuation for the 20 participants included: pneumonia (2 participants); nausea and dyspnoea; transient ischemic attack; hypertension; acute coronary syndrome; dysphagia; atrial fibrillation and non-cardiac chest pain; back pain; headache, sepsis, and lower gastrointestinal haemorrhage; angina pectoris; dizziness; sepsis; hip fracture; gastrointestinal disorders – other; peripheral sensory neuropathy and hypertension; febrile neutropenia; gastritis, pyrexia, constipation, embolism, and pharyngitis; enteritis and stomatitis; and palmar-plantar erythrodysesthesia syndrome.

Of the 20 participants who were reported as having discontinued the study due to a serious TEAE, 12 participants had Grade 3 TEAEs (pneumonia [2 participants]; nausea and dyspnoea; hypertension; dysphagia; atrial fibrillation; back pain; headache; hip fracture; peripheral sensory neuropathy and hypertension; febrile neutropenia; pneumonia [2 TEAEs], gastritis, embolism, and pharyngitis; and enteritis and stomatitis), 2 participants had Grade 4 TEAEs (sepsis and lower gastrointestinal haemorrhage; gastrointestinal disorders – other), and 1 participant had a Grade 5 TEAE. The fatal event was assessed as unrelated to treatment.

Nine TEAEs leading to discontinuation were assessed by the investigator as r**elated or possibly related to treatment** (ponatinib and/or chemotherapy). These included nausea (Grade 3), TIA (Grade 2), Hypertension (n=2; Grade 3), Atrial fibrillation (Grade 3), Angina pectoris (Grade 2), Gastrointestinal disorder (Grade 4), Peripheral Sensory Neuropathy (Grade 3), Pyrexia (Grade 2), Constipation (Grade 2), Palmar-Plantar Erythrodysesthesia Syndrome (Grade 2).

Study INCB 84344-201 - patients aged ≥ 60 years or ineligible for chemotherapy and SCT

As of the DCO date of 30 SEP 2021, 11 participants (25.0%) had a TEAE leading to discontinuation of ponatinib. Treatment-emergent AEs leading to discontinuation of treatment reported by ≥ 2 participants were acute coronary syndrome and pneumonia.

The following TEAEs leading to discontinuation of treatment were serious: acute coronary syndrome (3 participants), pneumonia (2 participants), and vascular graft occlusion, legionella infection, septic shock, cerebrovascular accident, and deep vein thrombosis (1 participant each).

Of the 12 participants who were reported as having discontinued the study due to TEAEs, 4 participants had Grade 3 TEAEs (acute coronary syndrome and legionella infection), 3 participants had Grade 4 TEAEs (myocardial ischemia, vascular graft occlusion, and cerebrovascular accident), and 3 participants had Grade 5 TEAEs (pneumonia and septic shock).

The events of infection were generally not assessed as related to treatment by the investigator. Cardiac and vascular disorders were generally considered treatment related.

Assessor's comment:

The overall treatment discontinuation rate due to TEAEs in the PACE study was 17.6%. In this study a higher proportion of patients with CP-CML (21.1%) discontinued treatment due to AEs than patients with AP-CML (11.8%) and BP-CML/Ph+ ALL (12.8%). Most of the TEAEs leading to discontinuation were considered related to treatment. Treatment-related TEAEs leading to discontinuation in ≥2 patients included platelet count decreased (18 patients; 4%), coronary artery disease (3 patients; 0.7%), and acute coronary syndrome, cardiac failure, cerebral infarction, pain in extremity, pericardial effusion, peripheral artery stenosis, and pulmonary embolism (2 patients each; 0.4%).

Thus, the discontinuation rates in Study AP24534-11-001 and Study INCB 84344-201 appeared to be somewhat higher than in the PACE trial, in particular in comparison to the discontinuation rates in the BP-CML/Ph+ ALL patients in PACE, indicating that the treatment might be less well tolerated in the proposed new target populations. However, treatment duration was shorter in the Ph+ ALL population in PACE than in Study AP24534-11-001 and Study INCB 84344-201, so a direct comparison is difficult.

3.5.9. TEAEs leading to dose modifications

Study AP24534-11-001 - Ponatinib + hyper CVAD

In Study AP24534-11-001, safety-related dose modifications for ponatinib were permitted for Grade 3 or 4 non-hematologic toxicity. Treatment could be held until the AE severity improved to Grade ≤ 1 and restarted at 30 mg once daily. The dose could be further decreased to 15 mg daily if needed for serious toxicities, or if found to be in the best interest of the participant and after discussion with the principal investigator (PI). Ponatinib dose modifications were also permitted during the intensive chemotherapy phase for management of ANC and platelets. Other dose modifications were to be discussed with the PI.

Data for dose *reductions* due to AEs are not available from Study AP24534-11-001. Per protocol, after the first 14 days in cycle 1, the dose was to be reduced from 45 mg to 30 mg in cycle 2 and then further reduced to 15 mg once a CMR was achieved.

Dose *interruptions* occurred for 23 of the 87 enrolled participants (26.4%). All dose interruptions were due to serious TEAEs. Serious TEAEs leading to treatment interruption for the 23 participants included: pneumonia (2 participants); urinary tract infection (2 participants); pancreatitis, embolism, and noncardiac chest pain; MI; skin infection; pyrexia; sepsis; pancreatitis; menorrhagia and pneumonia; febrile neutropenia; back pain; atrial fibrillation; cholecystitis, pneumonia, febrile neutropenia, and sinusitis; febrile neutropenia and pneumonia; febrile neutropenia and bacteraemia; pancreatitis, enterocolitis infectious, and abdominal pain; anaphylaxis and pancreatitis; pancreatitis and lipase increased; lipase increased; kidney infection; and menorrhagia.

Two participants experienced VOEs leading to dose interruption: MI and embolism. Both events were serious, Grade 3, and assessed as *unrelated* to study treatment by the investigator. Additionally, both VOEs occurred before the protocol amendment implementing the mandatory ponatinib dose reductions.

Study INCB 84344-201 - patients aged ≥ 60 years or ineligible for chemotherapy and SCT

In Study INCB 84344-201, ponatinib *dose reductions* (to 30 or 15 mg) were permitted if Grade 3 or 4 AEs occurred. In case of hematologic AEs concerning WBCs, platelets, and haemoglobin, dose reduction was permitted only after CHR was achieved.

Dose reductions due to an Adverse event were made in a total of 21 participants (47.7%). Events in the Skin and subcutaneous tissue disorders SOC were most common, and the most frequently reported (≥ 2 participants) TEAEs leading to a dose reduction were rash, erythema, skin exfoliation, lipase increased, ALT increased, and atrial fibrillation.

The following TEAEs leading to a dose reduction were serious TEAEs: arterial occlusive disease and atrial fibrillation, each reported in 1 participant.

As of the DCO date of 30 SEP 2021, a total of 20 participants (45.5%) had a TEAE leading to a temporary *interruption* of ponatinib treatment.

Events in the Skin and subcutaneous tissue disorders SOC were most common, and the most frequently reported (≥ 2 participants) TEAEs leading to a dose interruption were rash, ALT increased, cardiac failure, transaminases increased, and erythema.

The following TEAEs leading to a dose interruption were serious TEAEs: cardiac failure, (2 participants), and arterial occlusive disease, enterococcal sepsis, erythema, colitis ischemic, asthenia, rash, atrial fibrillation, embolism, leukopenia, and lung disorder (1 participant each).

Dose reductions were reported for 2 participants who had VOEs of chest pain (nonserious, Grade 2) and arterial occlusive disease (serious, Grade 3). Dose interruptions were reported for 2 participants who had serious VOEs of arterial occlusive disease (Grade 3) and embolism (Grade 4); the participant with the serious VOE of arterial occlusive disease subsequently had study drug discontinued due to a serious VOE of vascular graft occlusion. Five additional participants had study drug withdrawn due to VOEs, including 3 participants with acute coronary syndrome (all Grade 3), 1 participant with cerebrovascular accident (Grade 4), and 1 participant with myocardial ischemia (Grade 1). All events resolved after dose modifications and were considered *related* to ponatinib by the investigator.

3.5.10. Matching-Adjusted Indirect Comparison (MAIC)

Unanchored MAIC was used to estimate the relative safety between ponatinib versus imatinib as a 1L treatment option in two populations: patients who were eligible for HDT and SCT and patients noneligible for HDT and SCT.

The MAICs allowed to generate balancing statistical weights to apply to the index study (Study AP24534-11-001 and Study INCB 84344-201) to make them comparable to a given imatinib study hence mimicking a randomisation process between a ponatinib and an imatinib treatment arms. The MAIC was conducted using the methods described by Signorovitch et al (2012) following the guidelines of the National Institute for Health and Care Excellence (NICE).

A systematic literature review (SLR) and an indirect treatment comparison (ITC) were conducted to compare ponatinib against imatinib as a first-line treatment option in the two patient populations:

- The evaluation of ponatinib was based on the pivotal single-arm study, Study AP24534-11-001 (ponatinib in combination with hyper-CVAD for adults with Ph+ ALL). Data from Study AP24534-11-001 was compared with data from Study NCT00038610 (imatinib + hyper CVAD). This was a Phase 2, single-arm, single-center, open-label study of imatinib + hyper-CVAD conducted at the MDACC. Adult patients with de novo or minimally treated Ph+ ALL (ie, patients who received 1 or 2 courses of prior chemotherapy without TKIs) were enrolled in this study. Fifty-four participants were enrolled in this study. Participants received 8 cycles of therapy alternating imatinib + hyper-CVAD and imatinib + steroids. Participants in first complete response for whom a matched donor was available could receive SCT. Maintenance

imatinib therapy could be given for up to 24 months after the 8 cycles of chemotherapy (Table 49).

- No safety data were available for MAIC of Study INCB 84344-201 (patients ineligible for high dose therapy).

Table 49. Imatinib Studies Conducted in HDT-SCT Eligible Participants included in the MAIC analysis

NCT00038610 (Daver et al 2015, Thomas et al 2004)/AUS01 in the EMA EPAR/scientific discussion dossier of imatinib (Glivec 2022)	8 induction-consolidation courses of imatinib + hyper-CVAD alternated with imatinib + methotrexate + cytarabine	Study AP24534-11-001 participants not previously treated with TKI

EMA = European Medicines Agency; EPAR = European public assessment report; HDT = high-dose therapy; hyper-CVAD = hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; MAIC = matching-adjusted indirect comparison; PAIC = population-adjusted indirect comparison; SCT = stem cell transplantation; TKI = tyrosine kinase inhibitor.

Matching scenarios

The MAIC model specifications in the comparison of ponatinib + hyper-CVAD with imatinib + hyper-CVAD are detailed in the MAIC Report EVG-30650-03, which was provided in Module 5 of the submission, and will not be described in detail here.

Six models were investigated:

- Model 1 matched populations on all baseline characteristics available in both trials. The Effective sample size (ESS) obtained was too small to warrant further investigation, but the model converged.
- Model 2 was based on Model 1 and matched populations on all baseline characteristics available in both trials except for the proportion of participants with active disease at baseline. Compared to Model 1, Model 2 obtained a higher ESS and the model converged. The choice to not include the proportion of participants with active disease at baseline was conservative as it would bias the results against ponatinib since these participants with expected worse prognosis were more numerous in the weighted Study AP24534-11-001 population.
- Model 3 was based on Model 2, and performed a less granular population-adjustment, only retaining an adjustment on grouped range of value (ie, proportion of participants above a certain threshold value) instead of matching on both medians and grouped range of values. The ESS increased further and the model converged. This model was proposed in a sensitivity analysis.
- Model 4 matched populations on clinically validated prognostic factors or treatment-effect modifiers in Ph+ ALL. Compared to Models 2 and 3, population-adjustment on sex of participants, platelet counts, lactate dehydrogenase levels and hemoglobin levels was not conducted. The ESS increased and the model converged. This model was proposed as the base case.
- Model 5 was based on Model 4 and added an adjustment on the proportion of participants with active disease at baseline. Although the ESS achieved by this model was above the

prespecified threshold, a participant was given a large balancing weight which vastly increased the uncertainty of the results. As a result, this model was not investigated further.

- Model 6 matched populations on the 4 factors to prioritize according to clinical experts (age, ECOG PS, WBC count, and type of transcript). The ESS obtained was only comparable, numerically lower to Model 4, and as such this model was not investigated further.

Table 50 presents the baseline characteristics (in terms of proportion of the population with the specified characteristic) of the original Study AP24534-11-001 population and the weighted Study AP24534-11-001 population against reported characteristics for the participants treated with imatinib + hyper-CVAD in the NCT00038610 study. Following the population-adjustment, the population characteristics of the 2 studies at the treatment arm level were matched.

The proportion of participants with active disease at baseline was not included in the population-adjustment. As a result, the weighted Study AP24534-11-001 population and the NCT00038610 study population were imbalanced with respect to this factor: 0.9% of the weighted Study AP24534-11-001 sample had complete remission at baseline, as opposed to 16.7% of the NCT00038610 study population. However, not including this factor in the population-adjustment was expected to be conservative as it would bias the results in favour of imatinib, as participants in complete remission at baseline are expected to have a better prognosis compared to those with active disease at baseline.

Table 50. Baseline Characteristics of Study AP24534 11 001, the Weighted Study AP24534 11 001 Population, and the NCT00038610 Study

	Study AP24534-11-001	Study AP24534-11-001 Weighted	Study NCT00038610
Sample size	87	40.021	54
Median age (years)	46	51	51
Proportion of participants with ECOG PS of 0	0.253	0.130	0.130
Proportion of participants with CNS disease at baseline	0.069	0.130	0.130
Proportion of participants with WBC count (10^9/L) 30 or higher	0.103	0.370	0.370
Proportion of participants with WBC count missing	0.023	0.000	0.000
Proportion of participants with BCR-ABL1 transcript: m or p190	0.724	0.667	0.667
Proportion of participants with BCR-ABL1 transcript: missing	0.023	0.000	0.000
Proportion of participants in complete remission at start	0.207	0.009	0.167
Proportion of participants with prior TKI	0.207	0.000	0.000

BCR-ABL1 = breakpoint cluster region-Abelson 1; CNS = central nervous system; ECOG PS= Eastern Cooperative Oncology Group; MAIC = matching-adjusted indirect comparison; PS = performance status; TKI = tyrosine kinase inhibitor; WBC = white blood cell.

Results

After matching the weighted Study AP24534-11-001 population became comparable to the imatinib comparator population, and relative effects were estimated between the two treatments.

The following outcomes were considered for the safety analyses:

- Discontinuation due to AEs during the 8 induction/consolidation cycles
- Discontinuation due to AEs overall
- Death due to AEs

Odds ratios estimated from logistic regression models on safety outcomes are provided in Table 51 using data for ponatinib + hyper-CVAD before and following the population-adjustment against the reported data for imatinib + hyper-CVAD.

The odds ratios describe odds for ponatinib over odds for imatinib for the studied effects. As shown in Table 51, the odds ratios for discontinuations due to AEs and death due to AEs favoured imatinib-receiving patients. The MAH, however, points out that but none were statistically significant.

Table 51. Relative Safety Estimates for Observed and Weighted Ponatinib + Hyper CVAD vs. Imatinib + Hyper-CVAD (NCT00038610)

Outcome	Unadjusted Comparison (95% CI) [p-value]	Population-Adjusted Comparison (95% CI) [p-value]
Discontinuation due to AEs during the 8 induction/ consolidation cycles	OR: 7.67 (0.93, 63.57) [0.059]	OR: 5.33 (0.61, 46.53) [0.130]
Discontinuation due to AEs overall	OR: 2.39 (0.88, 6.50) [0.088]	OR: 1.96 (0.66, 5.86) [0.229]
Death due to AEs	OR: 3.23 (0.35, 29.55) [0.299]	OR: 3.22 (0.34, 30.22) [0.306]

AE = adverse event; CI = confidence interval; hyper-CVAD = hyper-fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone; MAIC = matching-adjusted indirect comparison; OR = odds ratio.

Limitations

Some assumptions were made in the analyses of discontinuation due to AEs. Adverse events that occurred during the 8 cycles of induction/consolidation period in Study AP24534-11-001 were defined as those that started before the first recorded date of a laboratory test performed as part of the maintenance period. The CSR definition was used to identify AEs that led to treatment discontinuation; it is unknown if it is fully comparable to the definition used in the NCT00038610 study.

The MAH suggests that as deaths due to AEs all occurred during the induction phase, differences in study duration was not a confounder in the determination of OR for this outcome.

MAH's conclusion

Not unexpectedly, a numerically more favourable safety profile was observed for imatinib, which may be explained by the higher potency of ponatinib also impacting its tolerance profile. However, it is important to note that no statistically significant results at the 0.05 threshold could be estimated.

Assessor's comment:

The results of the matching-adjusted indirect comparison (MAIC) indicate a clearly more favourable safety profile of imatinib+CVAD than for ponatinib+CVAD, in terms of odds ratios (ORs) for treatment discontinuations and death due to AEs, respectively. Although the confidence intervals are wide and the differences were not statistically significant, the MAH agrees that a lower tolerability to ponatinib may be expected and explained by the higher potency of ponatinib. The MAH points out that this modelling exercise have limitations and the results should be interpreted with caution. Nevertheless, the apparent increase in toxicity, not least deaths due to AEs for which the OR was 3.2 in favour of imatinib, is concerning, and further emphasizes that the lack of a control arm in Study AP24534-11-001 limits the possibility to draw informed conclusions on the tolerability of the new combination treatment.

3.5.11. Post-marketing data

Up to 13 Dec 2021, the estimated worldwide cumulative post-marketing patient exposure to ponatinib since 14 Dec 2012 (International Birth Date). This estimate assumes an average daily dose of 30 mg based on the current product labelling. The highest exposure is among patients treated in the EU and the US and Canada.

Because the post-marketing exposure is based on sales/shipment data, it is not currently possible to present the exposure by gender, age, dose, dose regimen form, or other factors. In addition, no non-interventional studies (including registries) investigating post-approval use have been conducted in special populations.

As of 13 Dec 2021, a total of 13,663 serious adverse drug reactions were reported in the 8474 post-marketing cases received for ponatinib (data on file). Most serious adverse drug reactions were reported from non-interventional studies and reports from other solicited sources. Ponatinib is also being used in compassionate use and named patient programs. On 24 MAR 2022, the requirement for additional monitoring of ponatinib was removed by EMA/CHMP. All post-marketing safety data are captured in the current product label).

3.5.12. Discussion on clinical safety (updated after assessment of the response to 1st RSI)

With the current application, the MAH seeks approval for two different indications, but both are for ponatinib as first-line treatment of patients with newly diagnosed Ph+ ALL:

1. ponatinib in combination with chemotherapy
2. as monotherapy with corticosteroid induction in patients unfit for intensive chemotherapy and allogeneic stem cell transplant

In support of each of the two indications the MAH submitted one, small single-arm study, respectively. From a safety perspective, the two studies cannot be considered directly supportive to each other, and therefore, in the discussion below, the safety data will be considered separately for each applied indication and study.

3.5.12.1. Ponatinib in combination with chemotherapy in newly diagnosed adult patients with Ph+ ALL

The safety profile of ponatinib as monotherapy has been evaluated in previous studies and can be considered well characterised. Ponatinib has, however, no previously approved indication in combination with chemotherapy.

To support the indication, the MAH submitted results of the Phase 2 Study AP24534-11-001. The safety population included 87 patients.

The study was initiated in year 2011, and patients in the study were treated with ponatinib in combination with high-dose chemotherapy (hyper CVAD). Ponatinib was originally administered at the 45 mg dose but after 37 patients were treated, the protocol was amended to reduce the dose of ponatinib to 30 mg per day from Cycle 2, with further reduction to 15 mg once a complete molecular response (CMR) was achieved. This amendment was based on the emerging knowledge of the prothrombotic effects of ponatinib, further described below, and mirrors the SmPC recommendations introduced for the previously approved indications to handle this risk.

The current safety information in the SmPC section 4.8 is primarily based on data from the PACE study, which was the registration study for ponatinib as second-line monotherapy in CML and Ph+ ALL. Keeping the limited database of 87 patients in mind, the data from Study AP24534-11-001 indicate a safety profile of ponatinib + hyper CVAD that is qualitatively similar to what was observed in the PACE trial, in terms of common adverse events (AEs), and treatment-related serious adverse events (SAEs).

The rate of some known adverse drug reactions (ADRs; e.g. febrile neutropenia and pneumonia), however, appeared to be higher in Study AP24534-11-001 than in previous monotherapy studies, which is anticipated at combination with chemotherapy. In response to the RSI, the MAH has updated the SmPC to reflect an increased risk of some ADRs when ponatinib is used in combination with chemotherapy.

Six deaths due to treatment-emergent adverse events (TEAEs) were reported, of which two were assessed as possibly treatment-related, as the cause of death was unclear in these cases. The two cases were, however, confounded by underlying co-morbidity.

The main concern in terms of ponatinib toxicity may be its pro-thrombotic properties. Ponatinib is associated with dose-dependent vascular occlusive events (VOEs), including arterial occlusive events (AOEs) and venous thromboembolic events (VTEs). The MAH compared the data on VOEs in Study AP24534-11-001 with the data from the PACE trial:

- In the PACE trial, overall AOEs occurred in 25% of ponatinib-treated patients with a minimum of 64 months follow-up, with serious adverse reactions occurring in 20% of patients. Some patients experienced more than one type of event. Adjusted for exposure, the rate of AOEs in the PACE trial was 13.8 per 100 Patient years at 53 months. In Study AP24534-11-001, overall AOEs occurred in 13.8% of patients. Adjusted for exposure, the incidence of AOEs was 7.9 per 100 patient years. Thus, the incidence seems to be lower than in the PACE trial. Contrary to the PACE trial, dose reductions to 30 mg after Day 14 in Cycle 1, and to 15 mg once CMR was achieved, were introduced in Study AP24534-11-001 during the course of the study, in line with the current recommendations in the SmPC, in order to minimise the risk for AOEs.
- In the PACE trial, VTEs (treatment-emergent frequencies) occurred in 6% of patients. Adjusted for exposure, the rate of TE-VTEs in the PACE trial was 2.75 per 100 Patient years. In Study AP24534-11-001, VTEs occurred in 12.6% of patients, or at an incidence of 7.6 per 100 patient years, which is a higher rate than in the PACE trial. VTEs are reported

ADRs also for e.g., MTX and Cyclophosphamide, and an increased risk at combination of ponatinib with chemotherapy must be taken into consideration. In response to the RSI, the MAH updated the SmPC sections 4.4 and 4.8 to reflect that the previously described VTE risk may be increased when ponatinib is used in combination with chemotherapy.

In study AP24534-11-001, a total of 20 participants (23.0%) experienced a serious TEAE leading to treatment discontinuation. All TEAEs leading to treatment discontinuation were serious. Nine TEAEs leading to discontinuation were assessed by the investigator as related or possibly related to treatment (ponatinib and/or chemotherapy). In the previous PACE trial, which was the basis for the original approval of Iclusig, the overall treatment discontinuation rate due to TEAEs was 17.6%. In patients with BP-CML/Ph+ ALL the rate was 12.8%. Thus, by crude comparison, the discontinuation rates in Study AP24534-11-001 appeared to be higher than in the PACE trial. However, treatment duration was shorter in the Ph+ ALL population in PACE than in Study AP24534-11-001, so a direct comparison is difficult.

All-in-all, the lack of a control arm in Study AP24534-11-001 limits the possibility to draw informed conclusions on whether the new combination is sufficiently well tolerated. The increased toxicity, including death by AEs, of ponatinib + chemotherapy compared with the external control group (imatinib + chemotherapy) selected by the MAH in the matching-adjusted indirect comparison (MAIC) is concerning, in particular in the light of the known pro-thrombotic potential of ponatinib. Furthermore, there was a multitude of protocol amendments including dose adjustments in this unblinded study, and it is unclear how the safety population might have changed over time. Considering that there are other available treatment options for the proposed target population, it is questioned whether the safety risks of ponatinib in combination with chemotherapy has been sufficiently well quantified to draw the conclusion the potential risks do no outweigh the imprecisely characterized efficacy of the treatment.

The MAH referred to a conference power point presentation, with data from the randomised, active controlled Study Ponatinib-3001 (PhALLCON), which compared ponatinib + reduced-intensity chemotherapy and imatinib (which is not associated with prothrombotic events) + reduced-intensity chemotherapy, in patients with newly diagnosed Ph+ ALL. Comparable tolerability to the two treatments appears to be demonstrated, as indicated by a similar rate of VTEs and a similar rate of treatment discontinuations in the two study arms. The rate of AOEs was low in both study arms. These data cannot presently be taken into account, as the complete study report is not available for assessment by the CHMP.

3.5.12.2. Ponatinib as monotherapy with corticosteroid induction in patients with newly diagnosed Ph+ ALL unfit for intensive chemotherapy and allogeneic stem cell transplant

To support the indication, the MAH submitted results of the Phase 2 Study INCB 84344-201. The safety population included 44 patients.

The data submitted in support of this indication is, thus, very limited. The safety assessment therefore relies mainly on previous data for ponatinib monotherapy. Here, the main concern is that the proposed indication involves a potentially more fragile population than the previously approved indications. An elderly population might, for example, include more patients with cardiovascular morbidity, being more prone to events related to the prothrombotic potential of ponatinib. Furthermore, the sought indication appears to include frailer patients than those patents included in the study, and therefore presumably less able to tolerate ponatinib. It is noted that eight participants (18%) did actually receive SCT as post-ponatinib therapy (according to ad-hoc analysis in CSR Addendum), despite the inclusion criteria ‘unfit for program of intensive therapy and allogeneic SCT’.

The patients included in the study had a median age of 66.5 years (range 26-85). There were 18 patients < 65 years old and 26 patients ≥ 65 years.

In Study INCB 84344-201, 95.5% of patients reported a treatment-emergent AE, and 84.1% reported a TEAE that was considered treatment-related by the investigator. The most common TEAEs occurred in the SOCs of Skin and subcutaneous tissue disorders (59.1%), General disorders and administration site conditions (47.7%), Gastrointestinal disorders (43.2%), and Musculoskeletal and connective tissue disorders (43.2%). The most common TEAEs by PT (reported in > 6 participants) were rash and asthenia, ALT increased, GGT increased, erythema, headache, and pyrexia. Overall, the pattern of common AEs did not obviously deviate from what is known from previous studies with ponatinib monotherapy, but the small sample size must be kept in mind.

A total of 23 participants (52.3%) had a serious TEAE. This number included five deaths due to AEs. One of the fatal TEAEs was considered by the investigator to be possibly related to ponatinib. The event was reported as sudden death on Day 671. The remaining four deaths were due to infections and were not considered treatment related.

Non-fatal SAEs were most commonly reported within the SOCs Cardiac disorders, Infections and infestations, and Vascular disorders. The most commonly reported PTs (reported in ≥ 2 patients) were acute coronary syndrome, arterial occlusive disease, atrial fibrillation, cardiac failure, and pneumonia. The most frequently reported *treatment-related* SAE by PT was acute coronary syndrome, reported in 3 participants.

Overall, 11 participants (25.0%) had a TEAE leading to discontinuation of ponatinib. Treatment-emergent AEs leading to discontinuation of treatment reported by ≥ 2 participants were acute coronary syndrome and pneumonia. Serious AEs leading to treatment discontinuation included cardiac and vascular disorders and infections, where the cardiac and vascular disorders were generally assessed as treatment-related, while infections were not.

In the previous PACE trial, which was the basis for the original approval of Iclusig, the overall treatment discontinuation rate due to TEAEs was 17.6%. In patients with BP-CML/Ph+ ALL the rate was 12.8%. Thus, by crude comparison, the discontinuation rates in Study INCB 84344-201 appeared to be higher than in the PACE trial. However, treatment duration was considerably shorter in the Ph+ ALL population in PACE (median 85.5 days) than in Study INCB 84344-201 (median 415 days), so a direct comparison is difficult.

Treatment-emergent VOEs were reported for 15 patients in Study INCB 84344-201 (34.1%). Some patients had more than one event. The most frequently reported PTs (≥ 2 participants) were chest pain, acute coronary syndrome, arterial occlusive disease, and embolism. There were 15 serious events in 9 patients of which 13 were considered related to treatment. There were no fatal, treatment-emergent VOEs but one fatal event (acute coronary syndrome) that occurred more than 30 days after treatment discontinuation. By comparison, in the PACE trial, the rate of TE-VOEs was 18.8% in Ph+ ALL patients (6/38 patients). Thus, the rate of VOEs seems higher in Study INCB 84344-201. However, again, the median duration of treatment in Ph+ ALL patients in PACE was considerably lower than in Study INCB 84344-201 (median 85 days, versus 415 days in Study INCB 84344-201). The average daily dose was fairly similar between the two trials. Thus, overall, exposure-adjusted rate of VOEs may not be higher in Study INCB 84344-201 than in PACE, but the small sample size precludes conclusions on the risk for VOEs in the proposed target population. A higher susceptibility to the prothrombotic effects of ponatinib cannot be excluded in an elderly population with a possibly higher prevalence of pre-existing cardiovascular disease. For example, atrial fibrillation is common in an elderly population, and a major cause of systemic embolism. The lack of data on Iclusig use in patients with atrial fibrillation should be added to section 4.4 of the SmPC.

The MAH argues that that in the context of the rarity of the Ph+ ALL indication, and specifically the subgroup of patients unfit for intensive chemotherapy and allo-HSCT, the safety profile of ponatinib in the targeted population is quantified with sufficient precision. Further, the MAH suggests that during the years since initiation of Study INCB 84344-201, knowledge on how to manage ponatinib toxicity has increased, which have led to lower rates of VOEs and lower rate of treatment discontinuations in latter studies. Indeed, in Study INCB 84344-201, there were no recommendation to reduce the dose to 15 mg at complete molecular response (CMR), while such a recommendation has been introduced in the SmPC, which may affect the rate of VOEs in clinical practice. On the other hand, the MAH has clarified that many patients in study INCB 84344-201 had dose reductions following response to treatment, as recommended in the SmPC. Altogether, this makes assessment of the tolerability in the target population, if dosed according to the proposed SmPC, difficult.

Taken together, given the limited size and exploratory nature of Study INCB 84344-201, it can be questioned whether the safety profile of ponatinib in the target population has been quantified with sufficient precision to be reliably compared to the imprecisely characterised efficacy metric in any population.

3.5.13. Conclusions on clinical safety

Ponatinib in combination with chemotherapy in newly diagnosed adult patients with Ph+ ALL.

The safety profile of ponatinib is non-trivial, including thrombotic events which previously prompted a referral questioning benefit/risk. All available data derive from a single-arm trial in combination with hyper-CVAD. This trial does not isolate drug effects on safety parameters or OS. As anticipated, the MAH's external comparison is indicative of a higher toxicity compared to imatinib. However, there are no internally or externally valid metrics of the risks related to the add-on use of ponatinib to chemotherapy. This includes its impact on overall survival.

Ponatinib as monotherapy with corticosteroid induction in patients with newly diagnosed Ph+ ALL unfit for intensive chemotherapy and allogeneic stem cell transplant

Data are derived from a single-arm study which do not isolate the contribution of ponatinib to adverse events, nor quantify its impact on OS. Given the very limited overall size of the safety database and the exploratory nature of the study, as well as the study population, it is not clear that the safety profile of ponatinib has been quantified in the proposed target population.

3.5.14. 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.

4. Risk management plan

The MAH submitted an updated RMP version (version 22.0) with this application. The (main) proposed RMP changes were the following:

- Addition of 1L Ph+ ALL data to the epidemiology of the indications and target populations.
- Inclusion of the 1L Ph+ ALL studies INCB 84344-201 and AP24534-11-001 demographics, baseline characteristics and overall extent of exposure.

- Addition of safety data from the 1L Ph+ ALL studies INCB 84344-201 and AP24534-11-001 to the characterization of important risks.
- Update of the post-marketing data as per a data lock point of 13 DEC2021.

No changes to the list of Safety concerns or the Pharmacovigilance plan were proposed.

The list of safety concerns is therefore as follows:

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

4.1. Overall conclusion on the RMP

☒The changes to the RMP are acceptable.

The overall conclusion on the RMP might, however, change based on the assessment of the response to the LoQ.

5. Update of the Product information

As a result of this variation section(s) 4.1, 4.2, 4.8 and 5.1 of the SmPC are being updated to reflect the new indications. The Package Leaflet (PL) is updated accordingly.

Please refer to appended, annotated Product Information.

5.1.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

6. Benefit-Risk Balance

6.1. Therapeutic Context

6.1.1. Disease or condition

The initially sought indication was:

"Iclusig is indicated in newly diagnosed adult patients with Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL)

- in combination with chemotherapy
- as monotherapy after corticosteroid induction in patients not eligible to receive chemotherapy-based regimens"

Subsequent to receipt of the first LoQ, the MAH has adapted the monotherapy indication as follows:

- as monotherapy with corticosteroid induction in patients unfit for intensive chemotherapy and allogeneic stem cell transplant.

6.1.2. Available therapies and unmet medical need

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

The NCCN guidelines recommend treatment with a TKI, along with chemotherapy in first line Ph+ ALL, and for older patients either reduced-intensity chemotherapy or steroid only in combination with a TKI. Similarly, ESMO guidelines recommends that a TKI should be combined with chemotherapy in front-line therapy.

In patients < 60 years with newly diagnosed Ph+ ALL, CMR rates with imatinib plus either vincristine/dexamethasone or hyper-CVAD, are reported to be 23% and 29%, respectively, after 2 cycles, with estimated 5-year OS of 43% and 48%, respectively (Chalandon et al 2015). After 1L treatment with imatinib plus steroid in 29 patients with Ph+ ALL, all patients reached CHR, and 1 of 27 evaluable patients reached CMR, and the median duration of hematologic response was 8 months (95% CI: 4-27) (Vignetti et al 2007).

In relapsed/refractory Ph+ ALL, resistant mutations in BCR-ABL1 may develop (Zabriskie et al 2014). The T315I mutation is the most common mutation associated with resistance to imatinib and dasatinib (Chiaretti and Foà 2015, Rousselot et al 2016). Ponatinib was designed to inhibit mutant forms of the BCR-ABL1 protein, including the T315I gatekeeper mutation.

6.1.3. Main clinical studies

Study AP24534-11-001

Data to support the sought indication "Iclusig is indicated in newly diagnosed adult patients with Ph+ ALL in combination with chemotherapy" are derived from an investigator-sponsored single-center study conducted at MD Anderson Cancer Center. It was a single-arm trial to evaluate the efficacy and safety of ponatinib in combination with Hyper-CVAD in newly diagnosed Ph+ ALL.

The key eligibility criteria included previously untreated Ph+ ALL, but also previously untreated lymphoid CML in accelerated or blast phase. Prior treatment with 1 to 2 courses of chemotherapy with or without other TKIs was allowed at study entry.

Primary endpoint was EFS rate at two years. Secondary endpoints were ORR, OS, and safety.

The MAH´s goal was to achieve a 2-year EFS rate >50%, in view of a historical reference 2-year EFS rate 0,49, from unpublished data, on the combination of hyper-CVAD plus imatinib or dasatinib. The sample size was not based on any statistical considerations. Analyses of efficacy measures are descriptive.

The analysis population was the enrolled population n=87, of which 86 patients had Ph+ ALL, and 1 patient had CML transforming into lymphoid blast phase.

First subject was enrolled 17 November 2011. At the time of data cut-off (14 December 2020), 24 participants were continuing to receive treatment.

Study INCB 84344-201

Data to support the sought indication "as monotherapy with corticosteroid induction in patients unfit for intensive chemotherapy and allogeneic stem cell transplant" is based on an initially investigator-sponsored study (GIMEMA consortium) for which the sponsorship was later transferred to Incyte. This was a multi-center study (22 study centers in Italy), single-arm, open-label, study of oral ponatinib in patients with previously untreated Ph+ ALL ≥ 60 years old or deemed at baseline not fit for intensive chemotherapy and SCT.

The study included patients with Ph+ ALL and no prior history of CML. Inclusion criteria comprised WHO performance status 0-2, and either age ≥ 60 years or age ≥ 18 years, but unfit for program of intensive therapy and allogeneic SCT.

CHR at 6 months was the primary endpoint. Pre-defined secondary endpoints included CCgR and CMolR at different timepoint, EFS, and OS. Duration of CHR was not included as an objective or endpoint in the protocol but was planned as an efficacy endpoint in the SAP.

The study hypothesis underlying the sample size calculation, was that 75% of subjects using ponatinib would be in CHR at 6 months. The null hypothesis, to be rejected in favour of the alternative, was based on a reference with CHR rate of 55% at 6 months with imatinib treatment (Vignetti et al 2007), as reported by the MAH. Efficacy parameters were summarized using descriptive statistics.

The full analysis set (n=44) included all participants enrolled in the study who received at least 1 dose of study drug.

This study enrolled participants from 04 DEC 2014 to 24 JAN 2017. Initial data cut-off date was 24 APR 2020, for the primary CSR. Final data cut-off date was 30 SEP 2021, for the CSR Addendum.

6.2. Favourable effects

Ponatinib in combination with chemotherapy in newly diagnosed adult patients with Ph+ ALL

Median duration of follow-up for EFS in all enrolled participants was 47.10 months (95% CI: 37.7, 70.7), 26 patients (29.9%) had an event, the median EFS was not reached.

The 2-year Kaplan-Meier estimated EFS rate was 75.1% (95% CI 64.0, 83.2) (primary endpoint).

Similar EFS rates were observed were observed in patients with CNS disease (n=6).

All 87 participants reached a CR (secondary endpoint) at any time. Of note, 18 of 21 the participants that had received 1-2 cycles of prior treatment showed a CR at baseline.

The complete molecular remission (CMR) rate was 78%.

With a median duration of follow-up for OS (secondary endpoint) of 45.1 months (95% CI: 36.50, 63.10), the median OS was NE (80.10, NE). Most participants (77.0%) were alive at last contact. The number of participants with events was 20 (23.0%)

Ponatinib and hyper-CVAD regimen resulted in Kaplan-Meier estimated 5-year EFS and OS rates of 68.1% and 73.8%.

Ponatinib as monotherapy after corticosteroid induction in patients unfit for intensive chemotherapy and allogeneic stem cell transplant

At 6 months, 38 of the 44 participants (86.4%) were in CHR (initial data cut-off date of 24 APR 2020 for Primary CSR) (primary endpoint).

It is noted that 40,9% of the participants were in CMR at the 6 months timepoint, and 54.5% were in CCgR.

In the CSR addendum, the longer duration of follow-up as of the 30 SEP 2021 data cut-off date, with a median duration of follow-up for OS of 63.2 months (95% CI: 60.45, 64.10), allowed for the evaluation of median duration of CHR and median OS (which had not previously been reached) and for the analyses of median duration of CMR and median EFS to be updated;

The median duration of CHR was 49.94 months (95% CI: 20.70, NE).

The median duration of CMR was 14.06 months (95% CI: 6.24, 21.91).

The median EFS was estimated as 29.54 months (95% CI: 18.27, 60.32).

The median OS was estimated as 61.67 months (95% CI: 25.82, NE).

Eight participants received SCT as post-study therapy after the first remission; 6 were alive at data cut-off, 2 participants died from relapse and disease progression (data cut-off date of 30 SEP 2021).

6.3. Uncertainties and limitations about favourable effects

Ponatinib in combination with chemotherapy in newly diagnosed adult patients with Ph+ ALL

While it is recognised that EFS at two years without treatment would be close to 0 in the absence of therapy, the study is a single-arm trial with add-on design. Therefore, neither this nor any other endpoint is capable of isolating the effect of ponatinib over and above hyper-CVAD in the pivotal trial. This is a fundamental deficiency which was pointed out in scientific advice.

The sample size in the submitted dossier (n=87) is limited and poses an uncertainty in terms of interpretation of results, including external validity and the possibility to validly compare with any external data***.***

It is considered questionable and unsuitable that the SAP was prepared post-data cut (but prior to the receipt of patient-level data) in this investigator-sponsored single-center trial. This study has an exploratory nature and is adapted during the in-study experience.

Ponatinib was given at 45 mg per day for 14 days in Cycle 1, and then after amended protocol, the ponatinib dose was reduced to 30 mg daily from Cycle 2, with further reduction to 15 mg once a CMR was achieved. Subsequent to receipt of the first LoQ, the proposed posology regarding dose reductions of ponatinib is deemed to be justified, since most participants received ponatinib as per the treatment scheme specified in the Protocol, which also may have included dose modifications due to toxicity. However, the text in the present SmPC, with respect to the total number of days for ponatinib treatment in first cycle, i.e, 14 days, has been changed from the original text and thereby must be considered incorrect. The MAH should reinstate the original posology of ponatinib during the first cycle .

After the maintenance period, per investigator discretion if patients were benefitting from therapy, continued daily ponatinib was permitted. In response to the RSI, the MAH has only partly justified the posology wording in SmPC section 4.2 to reflect the adequate duration of treatment and/or criteria for stopping treatment that was applied to the study population. Further clarification of particularly the criterion for stopping treatment is requested.

Ponatinib as monotherapy with corticosteroid induction in patients unfit for intensive chemotherapy and allogeneic stem cell transplant.

While the study endpoint would isolate an effect of ponatinib (in the absence of natural occurrence or co-treatment with agents that could induce the effect), the very small sample size, the limitation to Italian centers, causes unclarity of how the study population relates to any external cohort, contributes to concerns relating to generalizability of the reported results.

Patients that were included were 'unfit for program of intensive therapy and allogeneic SCT' However, the sought indication still appears to include frailer patients than those patents included in the study, and therefore presumably less able to tolerate ponatinib. It is noted that eight participants (18%) did actually receive SCT as post-ponatinib therapy (according to ad-hoc analysis in CSR Addendum), despite the inclusion criteria 'unfit for program of intensive therapy and allogeneic SCT'. This observation brings additional uncertainty to the external validity of the study. As outlined above, the MAH needs to justify the external validity of the generated data regarding the relationship between the study population and the proposed target population.

The MAH has submitted an indirect treatment comparison using historical controls that was not pre-planned. The external controls are nonetheless appreciated and in line with advice received (MPA, 18 November 2020) and should have been performed in an attempt to address challenges that comes with single-arm trials and may be useful in putting the ponatinib outcome from this single-arm trial into context. However, currently the comparison versus external controls is less useful since a major concern is to what extent study INCB 84344-201 owns external validity, and the selected external controls are not found be valid for matching and comparison.

The MAH has only partly justified the posology wording in SmPC section 4.2 to reflect the adequate duration of treatment and/or criteria for stopping treatment that was applied to the study population. Further clarification of particularly the criterion for stopping treatment is requested.

The MAH reports that a number of changes in the conduct of the study took place in addition to the protocol amendments. For example, treatment compliance was planned in the protocol, but drug compliance and drug accountability data were not collected during the GIMEMA sponsorship and were implemented first when Incyte became the sponsor two and a half year after finished enrollment. This issue is considered to reinforce the uncertainty of the external validity study results.

The SAP was written after the key study outcomes had been produced.

The MAH reports that no protocol deviations significantly affected the completeness, accuracy, and/or reliability of the study data or affected the study conclusions. However, protocol deviations were not collected in the database in the eCRF; the Incyte eCRF only captured reported eligibility criteria deviations. The MAH states that the overall protocol deviations were captured separately by Incyte's representative. The management of protocol deviations is considered to bring additional uncertainty to the generated data.

The duration of CHR curve has an intriguing plateau phase with two years without a single event. The MAH has been requested to comment. Moreover, the reasons for censoring in this analysis are unclear. In response to RSI, the MAH has partly clarified the plateau phase of the duration of CHR and also EFS curve. However, due to uncertainties regarding to what extent long-term follow-up implied systematically monitoring of events, and given the setting of a single-arm trial without no comparator, the presentation of CHR duration in the SmPC (5.1) should be from the primary analysis and not from the CSR Addendum**.**

6.4. Unfavourable effects

Ponatinib in combination with chemotherapy in newly diagnosed adult patients with Ph+ ALL

To support the indication, the MAH submitted results of the Phase 2 Study AP24534-11-001. The safety population included 87 patients.

Keeping the limited database of 87 patients in mind, the data from Study AP24534-11-001 indicate a safety profile of ponatinib + hyper CVAD that is qualitatively largely similar to what was observed in the original registrational study (the PACE trial) and what is previously described in the SmPC section 4.8.

The most commonly reported treatment-emergent adverse events (TEAEs) were, thus, within the SOCs haematological and gastrointestinal disorders and infections. The most common TEAEs by PT were febrile neutropenia, pyrexia, abdominal pain, headache, nausea, constipation, pneumonia, and diarrhoea. The most common TEAEs by PT that were assessed as *treatment-related* were nausea, diarrhoea, maculo-papular rash, peripheral sensory neuropathy, and abdominal pain.

Febrile neutropenia and pneumonia were very commonly reported (in 65.5% and 34.5% of patients, respectively), in Study AP24534-11-001. In the SmPC section 4.8, these reactions are reported as Common (i.e., 1-10%). Further, urinary tract infection was very commonly reported in Study AP24534-11-001 but is not previously listed as ADR. This added toxicity may be anticipated at combination with chemotherapy.

Six deaths due to treatment-emergent AEs were reported, of which two were assessed as possibly treatment-related, as the cause of death was unclear in these cases. One of these cases were classified as a veno-occlusive event (VOE, see below).

Treatment was discontinued due to TEAEs in 20 patients (23%) in Study AP24534-11-001. All TEAEs that led to treatment discontinuation were serious. Nine (10.7%) TEAEs leading to discontinuation were assessed by the investigator as related or possibly related to treatment (ponatinib and/or chemotherapy). These included nausea (Grade 3), TIA (Grade 2), Hypertension (n=2; Grade 3), Atrial fibrillation (Grade 3), Angina pectoris (Grade 2), Gastrointestinal disorder (Grade 4), Peripheral

Sensory Neuropathy (Grade 3), Pyrexia (Grade 2), Constipation (Grade 2), Palmar-Plantar Erythrodysesthesia Syndrome (Grade 2).

A total of 79 participants (90.8%) had at least 1 serious TEAE, including 77 participants (88.5%) with at least 1 that was Grade ≥ 3 in severity. The exposure-adjusted rate per 100 person-years was 2.86 (95% CI: 1.23, 4.49) with a total person-years of 27.64. This number of serious TEAEs includes fatal TEAEs.

The most frequently (≥ 15 participants) reported serious TEAEs by PT were febrile neutropenia, pyrexia, and pneumonia.

Ponatinib is known to be associated with dose-dependent VOEs, including arterial occlusive events (AOEs) and venous thromboembolic events (VTEs). In Study AP24534-11-001, overall AOEs occurred in 12 patients (13.8%). Adjusted for exposure, the incidence of AOEs was 7.9 per 100 patient years. Of the 8 participants with TE-AOEs that were assessed as related to treatment, the most common TE-AOEs by PT were angina pectoris (4 participants, 4.6%), followed by myocardial infarction (MI; 3 participants, 3.4%) and acute coronary syndrome and transient ischemic attack (1 participant, 1.1% each).

Grade 3 or 4 AOEs occurred in 4 participants (angina pectoris, 1 participant; and MI, 3 participants) and a Grade 5 AOE occurred in 1 participant (MI). Two dose interruptions for MI and embolism occurred before the protocol amendment implementing the mandatory ponatinib dose reductions.

VTEs occurred in 11 participants (12.6%), of which 8 (9.2%) had a VTE that was considered related to treatment and two (2.3%) had treatment-related TE-VTEs that were Grade ≥ 3. The reported terms were deep vein thrombosis (7 participants), embolism (3 participants) pulmonary embolism (2 participants), renal vein thrombosis (1 participant), both deep vein thrombosis and pulmonary embolism (1 participant), and one event of thrombophlebitis superficial. Serious TE-VTEs occurred in 6 participants (6.9%); 4 participants (4.6%) had serious TE-VTEs that were reported as treatment-related.

The serious VTE events reported in Study AP24534-11-001 appear to have been manageable as they did not lead to treatment discontinuation, and only in one case to treatment interruption. There was one death due to myocardial infarction.

Ponatinib as monotherapy with corticosteroid induction in patients with newly diagnosed Ph+ ALL unfit for intensive chemotherapy and allogeneic stem cell transplant

To support the indication, the MAH submitted results of the Phase 2 Study INCB 84344-201. The safety population included 44 patients.

In Study INCB 84344-201, 95.5% of patients reported a treatment-emergent AE, and 84.1% reported a TEAE that was considered treatment-related by the investigator. The most common TEAEs occurred in the SOCs of Skin and subcutaneous tissue disorders (59.1%), General disorders and administration site conditions (47.7%), Gastrointestinal disorders (43.2%), and Musculoskeletal and connective tissue disorders (43.2%). The most common TEAEs by PT (reported in > 6 participants) were rash and asthenia, ALT increased, GGT increased, erythema, headache, and pyrexia. Overall, the pattern of common AEs did not obviously deviate from what is known from previous studies with ponatinib monotherapy.

A total of 23 participants (52.3%) had a serious treatment-emergent AE. This number included five deaths due to AEs. One of the fatal TEAEs was considered by the investigator to be possibly related to ponatinib. The event was reported as sudden death on Day 671. Cause of death was not further

specified, but it was considered as a cardiovascular event. The remaining four deaths were due to infections and were not considered treatment related.

Non-fatal serious AEs (SAEs) were most commonly reported within the SOCs Cardiac disorders, Infections and infestations, and Vascular disorders. The most commonly reported PTs (reported in ≥ 2 patients) were acute coronary syndrome, arterial occlusive disease, atrial fibrillation, cardiac failure, and pneumonia. The most frequently reported *treatment-related* SAE by PT was acute coronary syndrome, reported in 3 participants.

Eleven participants (25.0%) had a TEAE leading to discontinuation of ponatinib. Treatment-emergent AEs leading to discontinuation of treatment reported by ≥ 2 participants were acute coronary syndrome and pneumonia.

SAEs leading to treatment discontinuation included cardiac and vascular disorders and infections, where the cardiac and vascular disorders were generally assessed as treatment-related, while infections were not.

Treatment-emergent VOEs were reported for 15 patients in Study INCB 84344-201 (34.1%). Some patients had more than one event. The most frequently reported PTs (≥ 2 participants) were chest pain, acute coronary syndrome, arterial occlusive disease, and embolism. There were 15 serious events in 9 patients of which 13 were considered related to treatment. In three cases ponatinib was withdrawn, and in two cases the event led to dose interruption. In the remaining cases the event did not lead to a change in treatment. There was no fatal TE-VOEs during the study reporting period; 1 fatal VOE (acute coronary syndrome) occurred more than 30 days after the participant discontinued ponatinib, and was therefore not considered treatment-emergent.

6.5. Uncertainties and limitations about unfavourable effects

Ponatinib in combination with chemotherapy in newly diagnosed adult patients with Ph+ ALL

The small size of Study AP24534-11-001, the lack of a control arm and a multitude of protocol amendments in an open study makes the quantification of risks related to ponatinib in combination with hyper-CVAD uncertain.

Acknowledging the limitations of the matching-adjusted indirect comparison with data from a study with imatinib + chemotherapy, it is concerning that the odds ratios for treatment discontinuations or death due to AEs were all in favour of imatinib.

Compared with ponatinib monotherapy (as observed in the PACE study, which was the basis for the initial approval of Iclusig), the rate of some known ADRs appeared to be higher in Study AP24534-11-001 and some additional ADRs were reported, which may be anticipated at combination with chemotherapy. Further, the rate of discontinuations due to TEAEs was 23% in Study AP24534-11-001, which appears to be somewhat higher than in the PACE trial, in particular in comparison to the discontinuation rates in the BP-CML/Ph+ ALL patients in PACE. However, direct comparisons are difficult due to differences in treatment duration and patient populations.

VTEs are reported ADRs also for e.g. MTX and Cyclophosphamide, and the potentially increased risk at combination of ponatinib with chemotherapy is addressed in the SmPC.

According to the study protocol, patients with pre-existing atrial fibrillation were excluded from Study AP24534-11-001. The additive thromboembolic risk of ponatinib in patients with atrial fibrillation is

unclear, as such patients have been systematically excluded from the study program The SmPC section 4.4. should be updated to reflect this. (**OC/SmPC**)

Ponatinib as monotherapy with corticosteroid induction in patients in patients with newly diagnosed Ph+ ALL unfit for intensive chemotherapy and allogeneic stem cell transplant.

The study submitted in support of this indication is very small (n=44) and explorative in nature. The safety assessment therefore relies heavily on previous data for ponatinib monotherapy. The main concern is, however, that the proposed indication involves a potentially more fragile population than the previously approved indications. Furthermore, the sought indication still appears to include frailer patients than those patents included in the study, and therefore presumably less able to tolerate ponatinib. It is noted that eight participants (18%) did actually receive SCT as post-ponatinib therapy (according to ad-hoc analysis in CSR Addendum), despite the inclusion criteria 'unfit for program of intensive therapy and allogeneic SCT'. The tolerability to ponatinib might, thus, potentially be lower in the proposed, new target population than in the populations covered by the previously approved indications *or* by the small-size Study INCB 84344-201.

In the previous PACE trial, the rate of VOEs was 18.8% in Ph+ ALL patients (6/38 patients). Thus, the rate of VOEs appears to be higher in Study INCB 84344-201 (34.1%). However, the median duration of treatment in Ph+ ALL patients in PACE was considerably lower than in Study INCB 84344-201 (median 85 days, versus 415 days in Study INCB 84344-201). Thus, overall, exposure-adjusted rate of VOEs may not be higher in Study INCB 84344-201 than in PACE, but assessment of the VOE risk in the new population is difficult. A higher susceptibility to the prothrombotic effects of ponatinib cannot be excluded in and an elderly population with a possibly higher prevalence of pre-existing cardiovascular disease.

According to the study protocol, patients with pre-existing atrial fibrillation were excluded from Study INCB 84344-201. The additive thromboembolic risk of ponatinib in patients with atrial fibrillation is unclear, as such patients have been systematically excluded from the study program The SmPC section 4.4. should be updated to reflect this.

In Study INCB 84344-201, there were no recommendation to reduce the dose to 15 mg at complete molecular response (CMR), while such a recommendation has been introduced in the SmPC. On the other hand, the MAH has clarified that many patients in study INCB 84344-201 had dose reductions following response. The differences between the study protocol, the actual doses used in the study and those recommended in the SmPC adds to the uncertainties regarding the ponatinib tolerability in the target population.

Altogether, it is questioned whether the potential risks with ponatinib in this population have been sufficiently well quantified.

6.6. Effects Table

Table 52. Effects Table for ponatinib in combination with chemotherapy in the treatment of newly diagnoses Ph+ ALL (data cut-off: 14 DEC 2020) Study AP24534-11-001

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects Study is ongoing.						

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Efficacy measures were descriptive and no formal statistical testing has been performed						
Event-free survival (EFS) (primary endpoint)	24 months	% (95% CI)	75.1 (64.0, 83.2)	N/A	Small sample size (n=86 with Ph+ ALL, 1 with CML). Open label, investigator-sponsored, single-center, single-arm, exploratory trial. Time dependent endpoints. Issues of external validity.	
Overall response rate (ORR)	All participants reached CR	% (n)	100 (87)	N/A	Eighteen of the 87 participants had a CR at baseline, all these 18 participants had received 1-2 cycles of prior anti-leukemia, shortly before inclusion.	

Effect	Short description	N	%	Control	Uncertainties / Strength of evidence
Unfavourable Effects					
All TEAEs	Occurring during or within 30 days after discontinuation of treatment	87	100	N/A	Small, uncontrolled study
Treatment-related TEAEs	Assessed as related to treatment (ponatinib or chemotherapy) by investigator	78	89.7	N/A	"
Serious TEAEs		79	90.8	N/A	" "
Serious treatment-related TEAEs		39	44.8	N/A	"
Grade 3-5 TEAEs		84	96.6	N/A	"
Treatment-related Grade 3-5 TEAEs		53	60.9	N/A	"
Serious Grade 3-5 TEAEs		77	88.5	N/A	"
Treatment-related Serious Grade 3-5 TEAEs		32	36.8	N/A	"
Serious TEAEs leading to dose interruption					
Serious TEAEs leading to discontinuation	All TEAEs leading to discontinuation were serious	20	23	N/A	"
On-study deaths	Deaths reported within 30 days of last dose	5	5.7	N/A	"
AOEs	Arterial occlusive events	12	13.8	N/A	"
AOEs Grade 3-4		4	4.6	N/A	"
AOEs Grade 5	PT: Myocardial infarction, death	1		N/A	"
VTEs	Venous thrombotic events	11	12.6	N/A	"

Effect	Short description	N	%	Control	Uncertainties / Strength of evidence
	(PTs: embolism [n=10] and thrombophlebitis superficial [n=1])				
VTEs Grade 3-4	No fatal VTE events	2	2.3	N/A	"
Gastro-intestinal disorders	SOC – all grades	68	78.2	N/A	"
Infections and infestations	SOC – all grades	63	72.4	N/A	"
Blood and lymphatic disorders	SOC – all grades	61	70.1	N/A	"
Nervous system disorders	SOC – all grades	61	70.1	N/A	"
General disorders and administration site disorders	SOC – all grades	52	59.8	N/A	"
Skin and subcutaneous tissue disorders	SOC – all grades	47	54.0	N/A	"

Abbreviations: N/A=not applicable, NE=not evaluable

Table 53. Effects Table for ponatinib as monotherapy after corticosteroid induction in newly diagnosed Ph+ ALL patients unfit for intensive chemotherapy and allogeneic stem cell transplant (data cut-offs: 24 APR 2020 Primary CSR, 30 SEP 2021 CSR Addendum) Study INCB 84344-201

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects Study is finalized Efficacy measures were descriptive and no formal statistical testing has been performed						
Primary CSR						
Complete hematologic response (CHR) at 6 months (primary endpoint)	Proportion of participants who were in CHR at 6 months	%	86.4	N/A	Sample size (n=44). Open label, single-arm, exploratory trial,	
CSR addendum						
Median duration of CHR	Median 95% CI	months	49.94 (20.70, NE)	N/A	Duration of CHR was not included as an objective nor endpoint in the protocol Note, time dependent endpoint in single-arm trial.	
Median	Median 95%	months	29.54	N/A	Note, time dependent endpoint	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
event-free survival (EFS)	CI		(18.27, 60.32)		in single-arm. No claims can be based on this endpoint.	

Effect	Short description	N	%	Control	Uncertainties / Strength of evidence
Unfavourable Effects					
All TEAEs	Occurring during or within 30 days after discontinuation of treatment	42	95.5	N/A	Small, uncontrolled study
Treatment-related TEAEs	Assessed as related to ponatinib by investigator or missing causality assessment	37	84.1	N/A	"
Serious TEAEs		23	52.3	N/A	" "
Grade 3-5 TEAEs		35	79.5	N/A	"
TEAEs leading to dose reduction		21	47.7	N/A	"
TEAEs leading to dose interruption		20	45.5	N/A	"
TEAEs leading to discontinuation	All TEAEs leading to discontinuation were serious	11	25.0	N/A	"
On-study deaths	Deaths reported within 30 days of last dose	5	5.7	N/A	"
Treatment-emergent VOEs	Vascular occlusive events	15	34.1	N/A	"
Treatment-emergent VOEs Grade 3-4	One fatal VOE occurred more than 30 days after treatment discontinuation	9	20.4	N/A	"
Skin and subcutaneous tissue disorders	SOC – all grades	26	59.1	N/A	"
General disorders and administration site disorders	SOC – all grades	21	47.7	N/A	"
Gastro-intestinal disorders	SOC – all grades	19	43.2	N/A	"
Musculoskeletal and connective tissue disorders	SOC – all grades	19	43.2	N/A	"

Abbreviations: N/A=not applicable, NE=not evaluable

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

Ponatinib in combination with chemotherapy in newly diagnosed adult patients with Ph+ ALL

The MAH proposes an indication for newly diagnosed adult patients with Ph+ ALL in combination with chemotherapy. This is based on a single-arm study from a single-center, where ponatinib was added to hyper-CVAD in 86 patients with Ph+ ALL, plus one participant with CML transforming into lymphoid blast phase.

In a single-arm study with add-on design, there is no efficacy metric that isolates drug effects. Moreover, some patients in the study received prior treatment with chemotherapy. Further, in this exploratory study, there were multiple protocol amendments despite the open label, including a sample size expansion as well as changed dosing of ponatinib and chemotherapy agents.

For the reasons given above, it is not clear that the experience reported in the single-arm, single-center study can reasonably be compared to any external cohort. While the activity of ponatinib in this disease setting is not questioned, an internally or externally valid metric of the effect size of the test agent cannot be derived based on the data submitted.

The safety profile of ponatinib is non-trivial, including thrombotic events which previously prompted a referral questioning benefit/risk. As anticipated, the MAH's external comparison is indicative of a higher toxicity compared to imatinib. However, there are no internally or externally valid metrics of the risks related to the add-on use of ponatinib to chemotherapy.

In summary, for the reasons given above, neither the beneficial nor the unfavourable effects of ponatinib in the proposed use can be reasonably quantified, and a determination of the balance of benefits and risks is consequently not possible.

These considerations result in the following major objection:

Study AP24534-11-001 is a single arm, single centre trial of exploratory nature. It indicates the activity of ponatinib but does not allow for a quantification of the benefits and risks as add-on to chemotherapy. Therefore, it does not allow for a conclusion on the B/R balance.

With respect to the applicant's claim for use with any chemotherapy, it is agreed that the results from the combination with hyper-CVAD can be extrapolated to other intensive backbone chemotherapies. However, results cannot be extrapolated to reduced-intensity chemotherapies, since the patient population, and therefore the safety profile, of ponatinib will differ.

Ponatinib as monotherapy with corticosteroid induction in patients in patients with newly diagnosed Ph+ ALL unfit for intensive chemotherapy and allogeneic stem cell transplant

Due to the small sample size of the single-arm pivotal trial (N=44), its exploratory nature, as well as the limitation of study conduct to centers in the same country, the relevance of the effect size in Study INCB 84344-201 to any definable population is unclear.

The sought indication appears to include frailer patients than those patents included in the study, and therefore presumably less able to tolerate ponatinib. While the activity of ponatinib as such is not

disputed, the MAH should justify for what, if any, population, the efficacy metrics of the INCB 84344-201 study have external validity.

Given the very limited overall size of the safety database, the exploratory nature of the study, as well as the study population which may be more fit than the target population (exemplified by the fact that 8/44 patients "unfit for ASCT" did receive SCT), the safety profile of ponatinib in the target population has not been quantified with sufficient precision to be reliably compared to the imprecisely characterised efficacy metric in any population. Thus, similar to use in combination with chemotherapy, the balance of benefits and risks for the proposed cannot be appropriately weighed.

These considerations result in the following major objection: Due to the small sample size of the single-arm Study INCB 84344-201 (N=44), its exploratory nature, as well as the limitation of study conduct to centres in the same country, the relevance of the recorded effect size to any definable target population is unclear. While the activity of ponatinib as monotherapy is not disputed, the MAH should justify that the efficacy and safety profile has been characterised to an extent that allows for a conclusion that the benefits of ponatinib outweighs its risks with the intended use in patients unfit for intensive chemotherapy and allo-HSCT.

6.7.2. Balance of benefits and risks

The balance of benefits and risks cannot be properly ascertained based on the submitted data. Therefore, the benefit-risk balance cannot be deemed positive.

6.8. Conclusions

The overall B/R is negative in the sought indication at the present time.