21 March 2013
EMA/CHMP/220290/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Iclusig

International non-proprietary name: PONATINIB

Procedure No EMEA/H/C/002695/0000

Note

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

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Product information

Name of the medicinal product:	Iclusig
Applicant:	ARIAD Pharma Ltd 2 Temple Back East Temple Quay Bristol, BS1 6EG UNITED KINGDOM
Active substance:	ponatinib
International Nonproprietary Name/Common Name:	ponatinib
Pharmaco-therapeutic group (ATC Code):	L01XE – Protein kinase inhibitors L01XE24
Therapeutic indications:	Iclusig is indicated in adult patients with • chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib; who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation • Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.
Pharmaceutical form:	Film-coated tablet
Strengths:	15 mg and 45 mg
Route of administration:	Oral use
Packaging:	bottle
Package sizes:	15 mg: 60 tablets and 180 tablets 45 mg: 30 tablets and 90 tablets

Table of contents

List of abbreviations

Abbreviation or Acronym	Meaning
ADME	Absorption, Distribution, Metabolism and Excretion
ALL	acute lymphoblastic leukaemia
AML	acute myeloid leukaemia
AP	accelerated phase
AP-CML	Accelerated Phase- Chronic Myeloid Leukaemia
API	Active Pharmaceutical Ingredient
AUC	area under the curve
BCR-ABL	Break point Cluster Region –ABeLson, the protein that causes CML and Ph+ ALL)
BCS	Biopharmaceutics Classification System
BP	blast phase
BP-CML	Blast Phase- Chronic Myeloid Leukaemia
CCyR	Complete Cytogenetic response
CHR	Complete Haematological Response
CLL	chronic lymphocytic leukaemia
CML	chronic myeloid leukaemia
CMR4.5	Complete Molecular Response
CP	chronic phase
CP-CML	Chronic Phase- Chronic Myeloid Leukaemia
CQA	Critical Quality Attribute
DLT	dose limiting toxicity
DoE	Design of experiments
DSC	Differential scanning calorimetry
EAP	expanded access program
ECOG	Eastern Cooperative Oncology Group
FMEA	Failure Mode Effects Analysis
FT-IR	Fourier Transformed Infrared spectroscopy
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonization
INN	International Non-proprietary Name
IPC	In Process Control
IR	Infrared spectroscopy
KF	Karl Fisher titration
LC-MS	liquid chromatography-mass spectrometry
LOD	Limit of detection
LOQ	Limit of quantification
MHR	Major Haematological Response
MCyR	Major Cytogenetic response
MMR	Major Molecular Response
MR4	Molecular response 4
MTD	maximum tolerated dose
NAS	New Active Substance
ND	Not detected
NEL	No evidence of leukaemia
NLT	not less than
NMR	nuclear magnetic resonance spectroscopy
NMT	not more than
NOEL	no observed effect limit
NP	not performed
NR	not reported or not required
NT	not tested
PCyR	Partial Cytogenetic response
Ph+	Philadelphia chromosome positive
Ph. Eur.	European Pharmacopoeia

PTCL	Peripheral T cell lymphoma
QbD	Quality by Design
QP	Qualified person
QTTP	Quality Target Product Profile
R/I	resistant or intolerant
SD	standard deviation
TG	Thermogravimetry
TKI	tyrosine kinase inhibitor
USAN	United States Adopted Name
USP	United States Pharmacopeia
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant ARIAD Pharma Ltd submitted on 30 August 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Iclusig, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 16 February 2012.

Iclusig, was designated as an orphan medicinal product EU/3/09/715 and EU/3/09/716 on 02 February 2010. Iclusig was designated as an orphan medicinal product in the following indications:

- Treatment of acute lymphoblastic leukaemia;

- Treatment of chronic myeloid leukaemia.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designations of Iclusig as an orphan medicinal product in the approved indications. The outcome of the COMP review can be found on the Agency's website ema.europa.eu/Find medicine/Rare disease designations.

The applicant applied for the following indication: Iclusig is indicated in adult patients with chronic phase, advanced phase, or blast phase chronic myeloid leukaemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant or intolerant to prior tyrosine kinase inhibitor therapy.

The legal basis for this application refers to:

New active substance (Article 8(3) of Directive No 2001/83/EC)

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0131/2012 on the agreement of a paediatric investigation plan (PIP).

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

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance ponatinib contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice/Protocol Assistance

The applicant received combined Scientific Advice/Protocol Assistance from the CHMP on 24 June 2010 and COMP on 8 July 2010 and a follow-up from the CHMP on 19 January 2012 and COMP on 8 February 2012. The applicant received an additional Protocol Assistance from the CHMP on 17 March 2011. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier. The applicant did not seek scientific advice at the CHMP.

Licensing status

Iclusig has been given a Marketing Authorisation in United States of America on 14 December 2012.

Manufacturer responsible for batch release

Haupt Pharma - AMAREG GmbH
Donaustaufer Strasse 378
D-93055 Regensburg
Germany

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Ian Hudson **Co-Rapporteur: Bengt Ljungberg**

- The application was received by the EMA on 30 August 2012.
- Accelerated Assessment procedure was agreed-upon by CHMP on 25 July 2012.
- The procedure started on 19 September 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 December 2012 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 December 2012 (Annex 2). In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 17 January 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 18 January 2013 (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 February 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of

Questions to all CHMP members on 5 March 2013 (Annex 5).

- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 15 March 2013 (Annex 6).
- During the meeting on 21 March 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Iclusig.
- The CHMP adopted a report on similarity of Iclusig on 21 March 2013 (Appendix 1)

2. Scientific discussion

2.1. Introduction

Problem statement

Chronic myeloid leukaemia (CML) is a clonal myeloproliferative disorder representing about 15% to 20% of adult leukaemias (Deininger et al, 2000; Pinilla-Ibarz et al, 2008). The underlying cause of CML is the BCR-ABL fusion oncoprotein, which results from a reciprocal t (9; 22) chromosomal translocation in hematopoietic stem cells. This chromosomal abnormality, known as the Philadelphia chromosome (Ph+), is present in about 95% of all patients with CML, as well as about 20% to 25% of adult patients with acute lymphoblastic leukaemia (ALL). The translocation leads to the fusion of the Breakpoint Cluster Region (BCR) coding sequence with the tyrosine kinase coding region of ABL. This fusion event results in the constitutive activation of ABL kinase activity. BCR-ABL activates multiple downstream pathways that contribute to the growth and survival of cells (Hazlehurst et al, 2009).

Chronic myeloid leukaemia is typically a triphasic continuum of disease with a chronic phase (CP-CML), accelerated phase (AP-CML), and blast phase (BP-CML)—characteristics of the disease and prognosis are different for each phase. Chronic is the longest phase, and can last over 10 years in some patients (Padmanabhan et al, 2008). However, if transition to AP-CML occurs, median survival is typically limited to under a year, while patients in BP-CML (which resembles acute leukaemia) usually live for only a few months. Most patients are diagnosed in CP-CML and may be asymptomatic or present with fatigue, anaemia, weight loss, night sweats, or splenomegaly.

Acute lymphoblastic leukaemia (ALL) is a malignant proliferation of lymphoid cells. The majority of cases of ALL show chromosomal and genetic abnormalities, and approximately 25% of adult cases of ALL are Ph+. The presence of the BCR-ABL translocation confers an adverse prognosis (Radich, 2001).

Current treatment guidelines (European LeukemiaNet and National Comprehensive Cancer Network) recommend treatment with Tyrosine Kinase Inhibitors (TKIs). In Europe the following TKIs are currently approved for the treatment of CML and Ph+ ALL: Glivec (imatinib); Sprycel (dasatinib); and Tasigna (nilotinib).

Treatment for CML was significantly advanced in 2001 following the approval of imatinib. Since then, targeted therapy with imatinib in newly diagnosed patients has become standard. With imatinib the complete cytogenetic response (CCyR) rate was reported as 76% (O'Brien et al., 2003). Dasatinib and nilotinib have also been approved for the treatment of patients who are or become resistant to imatinib therapy. These drugs yield complete cytogenetic response rates (CCyR) from 30%-50% (Talpaz et al., 2006; Kantarjian et al., 2006). Resistance to TKI therapy continues to be a significant challenge in the

treatment of CML. At present, there is no standard approach to treat the CML patient who has been treated unsuccessfully with both imatinib and then either with dasatinib or nilotinib.

The best understood mechanism of resistance to TKI therapy is the development of point mutations in the BCR-ABL kinase domain. More than 100 different mutations in the kinase domain of ABL have been discovered and have been shown to be responsible for 40% to 50% of the resistance to existing TKIs (Jabbour et al., 2009). The detection of kinase domain mutations even early in disease is adversely prognostic (Khorashad et al., 2008), is higher in accelerated phase (AP)/blast phase (BP) compared with chronic phase (CP) and increases with the duration of disease (Quintas-Cardama & Cortes, 2008). For patients who fail imatinib therapy, the frequency of BCR-ABL mutations ranges from 40% to 90%, depending on the phase and method of detection (Quintas-Cardama & Cortes, 2008).

The most common single resistant mutation, which occurs in approximately 15% of patients who develop resistance to imatinib (Quintas-Cardama & Cortes, 2008), is a transition point mutation at position 944 of the BCR-ABL gene, resulting in a substitution of isoleucine (I) for threonine (T) at position 315 of the protein: designated T315I, a "gatekeeper" mutation. The T315I mutation accounts for 15%-20% of all mutations observed in refractory CML (Nicolini et al, 2009).

Although dasatinib is effective against some mutations that confer resistance to imatinib therapy, and nilotinib also treats some imatinib-induced mutations, no approved drug inhibits T315I mutation.

However, not all patients who fail therapy carry detectable resistance mutations. Mutations are undetectable in a substantial proportion of patients who fail imatinib. In many of these patients, non BCR ABL driven mechanisms of resistance are likely contributing to resistance.

About the product

Ponatinib is a tyrosine kinase inhibitor, produced by a computational and structure-based approach to the development of a small molecule TKI. Ponatinib was designed with the purpose of potently inhibiting the kinase activity of native BCR-ABL, and all mutant variants, including 'gatekeeper' T315I.

The applicant claimed the approval for the following indication:

Iclusig is indicated in adult patients with chronic phase, advanced phase, or blast phase chronic myeloid leukaemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant or intolerant to prior tyrosine kinase inhibitor therapy.

The final indication following CHMP review of this application is:

Iclusig is indicated in adult patients with

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

Type of Application and aspects on development

This application has been submitted in accordance with the Article 8(3) of Directive 2001/83/EC, concerning a new active substance in the centralised procedure containing administrative, quality, non-clinical and clinical data.

According to Article 3(1) and point 4 of the Annex of Regulation (EC) No 726/2004, referring to an orphan designated medicinal product, this application falls under the mandatory scope for a centralised procedure application.

This application has been accepted for accelerated assessment by the CHMP on 25/07/2012.

The applicant received protocol assistance from CHMP and COMP:

EMEA/H/SA/1556/1/2010/PA/SME/III and EMEA/H/SA/1556/2/2010/PA/SME/III
These involved the non-clinical program, the clinical pharmacology studies planned, and the pivotal phase II study design. The phase II single arm study discussed is relevant to the indication applied for in this application.

EMEA/H/SA/1556/3/2011/PA/SME/III
This scientific advice dealt with quality issues in relation to the development and manufacture of the drug substance and product.

EMEA/H/SA/1556/1/FU/1/2011/PA/SME/III
This advice dealt with the requirements for additional non-clinical data in relation to the currently applied indications. In addition advice was also given regarding the conduct and design of a phase III clinical study comparing ponatinib with imatinib in the first line indication in chronic phase chronic myeloid leukaemia (CML-CP). This indication is not applied for in this application.

In the adopted SAWP advice, it was stated that

1) major cytogenetic response or major molecular response rates are both acceptable surrogate primary endpoints in CML-CP but should also include a time endpoint to show durability;

2) if the response rate is convincing a pivotal single arm Phase 2 trial might be acceptable for T315I+ CP-CML;

3) a non-comparative design may not be acceptable for patients resistant or intolerant to a second-line agent without a BCR-ABL mutation; if efficacy of AP24534 was comparable to that of approved second-line TKIs in terms of MCyR or MMR, single arm studies in the populations to be studied would support licensure if tolerability and toxicity also were similar.

A paediatric investigation plan (PIP) has been agreed for, in the indication to treat children with Chronic (CP), accelerated (AP), or blast phase (BP) CML who are resistant or intolerant to prior tyrosine kinase (TKI) therapy.

A product-specific waiver was granted for the treatment of chronic myeloid leukaemia and acute lymphoblastic leukaemia in children from birth to less than 1 year of age, on the basis that these diseases do not normally occur in the specified paediatric subset.

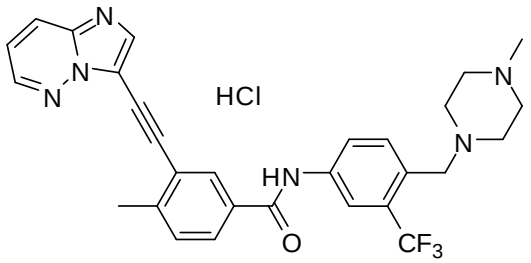
2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 15 mg and 45 mg of ponatinib (as hydrochloride) as the active substance. The other ingredients are lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal anhydrous silica and magnesium stearate. The film-coating consists of talc, macrogol 3000, poly(vinyl alcohol) and titanium dioxide (E171). The proposed packaging for the tablets consists of HDPE bottles with polypropylene closures.

2.2.2. Active Substance

Ponatinib is an off-white to yellow powder, not hygroscopic and soluble in organic solvents such as 2,2,2-trifluoroethanol, dimethyl sulfoxide, N,N-dimethylacetamide, sparingly soluble in methanol and slightly soluble in ethanol. In addition, the active substance is slightly soluble in aqueous solutions and high soluble in acid aqueous solutions. The chemical name is 3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoro methyl)phenyl}benzamide hydrochloride. The molecular formula is $C_{29}H_{28}ClF_3N_6O$ and has the following chemical structure:



Ponatinib has no chiral carbon atoms. Only one polymorphic form is consistently produced and used during the manufacture of the finished product.

Manufacture

Ponatinib is synthesized in four main steps using commercially available and well defined starting materials. The final active substance is purified by crystallisation. The manufacturing process is described in detail and has been developed using a combination of an enhanced development process with a number of design of experiment (DOE) studies carried out along with conventional univariate studies. The purpose was to better understand the process and to propose design spaces in terms of processing ranges for some of the most important unit operations.

The DOE studies were carried out using fractional or full factorial designs. Full details of the studies have been presented. This includes the factors that were evaluated along with the responses and a statistical evaluation of the results.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed Design Spaces.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

A comprehensive discussion on impurities and residual solvents was presented and the results were well within the limits set by the ICH guidelines Q3A and Q3C.

The purified active substance is packed in double polyethylene (LDPE) bags.

Specification

The active substance specification includes tests for: appearance, identification (FT- IR; HPLC), chloride identity, chloride assay, assay (HPLC), impurities (HPLC), residual solvents (GC), solid form confirmation

(XRPD, Ph.Eur.), heavy metals, particle size distribution (Ph.Eur.), residual metal catalysts (Ph.Eur.) and water content (Ph.Eur.).

A detailed description for all analytical methods was provided. Full method validation data was also provided for the in-house analytical methods in accordance with the relevant ICH Guidelines. The analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data are provided on twenty four pilot batches and four production batches produced by the proposed synthetic route, and the batch analysis data show that the active ingredient can be manufactured reproducibly. All results are within the specifications and consistent from batch to batch.

Stability

Three production scale batches of the active substance packed in the intended commercial packaging (LDPE bags) from the proposed manufacturers were put on stability testing as per ICH conditions: under long term (25°C/60%RH) for up 24 months, under intermediate conditions (30°C/60%RH) and accelerated (40°C/75%RH) for up 6 months. The active substance used in the primary stability studies was manufactured according to the commercial process.

The following parameters were tested: appearance, assay (HPLC 98.0– 102.0%), impurities (HPLC), residual solvents (GC), solid form confirmation (XRPD, Ph.Eur.), water content and microbial quality (Ph.Eur.).

Forced degradation studies were conducted by exposing the active substance to high temperature, acid, base and oxidative conditions. It was noted that only minor degradation of the active substance was observed under exposure to heat, but significant degradation was observed in acid and under oxidative conditions.

Photostability testing following ICH guidelines Q1B was performed. The results showed that there are no significant changes for any of the evaluated parameters established for the stability studies.

The stability results indicate that the active substance is stable at controlled room temperature. The results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim of the pharmaceutical development was to obtain immediate release film-coated tablet.. The proposed strengths of tablets (15mg and 45mg) are of different sizes. The excipients used are common for these types of dosage form and are of pharmacopoeial quality.

During drug development three different pharmaceutical forms have been developed: drug-in-capsule (no other excipients were used in this formulation), capsules, 15 mg and 45 mg film coated tablets.

The composition of the formulated capsules and tablets were very similar and both were manufactured using a dry blend to produce two dose-weight proportional capsule or film-coated tablet. Capsules were used only in the early dose-escalation portion of the phase I clinical trial. The need for a commercial dose of 45 mg was identified during the phase I clinical trial. Bioequivalence studies were not required in order

to demonstrate similarity between capsules and the proposed commercial formulation. The discriminatory power of the dissolution method has been demonstrated during the drug development.

The finished product have been developed using an enhanced approach with design of experiment studies (DOE) carried out on some aspects of the process. This was done to gain a better understanding of the product and manufacturing process.

Detailed information has been provided regarding the formulation development and manufacturing history in terms of the formulation, process and sites and extensive batch data has been provided which confirms the consistency/uniformity of the products.

The primary packaging proposed is adequately described (HDPE bottles closed with polypropylene screw caps). The packaging materials comply with Ph.Eur. requirements and are adequate to support the stability and use of the product.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Manufacture of the product

The manufacturing process consists of the following main steps: blending, compression, film coating and packaging. The process is considered to be a standard manufacturing process.

As already mentioned Design space is applicable to the compression step in terms of acceptable processing ranges (compression force and press speed).

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process and it is able to consistently produce a finished product of the intended quality. The in-process controls are adequate for this pharmaceutical form.
The batch analysis data on three batches per strength show that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product specification

The finished product release specification includes appropriate tests for appearance (visual), identification (UV), assay (HPLC), impurities (HPLC), content of uniformity (Ph.Eur.), and dissolution (HPLC).

Batch analysis results in nine commercial batches, of 15 mg film-coated and eight batches, of 45 mg film-coated tablets, confirm consistency and uniformity of manufacture and indicate that the process is under control.

Stability of the product

Stability data of three batches of each strength stored under long term conditions for 18 months at 25ºC/60%RH and 30°C/75% RH and for up to 6 months under accelerated conditions at 40ºC/75%RH according to ICH guidelines. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The stability samples were analysed for appearance, dissolution, assay (HPLC) and impurities (HPLC).

In addition, the photostability of one batch of film-coated tablets was evaluated in accordance with ICH guideline Q1B (Photostability Testing of New Drug Substances and Products). No significant changes were observed in the stability parameters tested except appearance. Tablets exposed to direct light changed from white to light yellow and failed specification.

The proposed shelf-life of 24 months with the labelled storage condition "Store in the original package in order to protect from light" has been justified by stability data provided.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The Applicant used Quality by Design principles in its development approach for both the active substance and finished product. A design space was claimed for some steps of the manufacturing process of the active substance. The potential impurities, by products of the synthesis and degradation products, have been discussed in detail and do not raise any safety concern. The control test and specifications for the active substance have been adequately established. There are no novel excipients used in tablet formulation and all excipients are compendial in line with the requirements of the current Ph.Eur. monographs. The manufacturing process of the film-coated tablets was considered to be a standard manufacturing process. A Design Space has been developed for the compression step. The results of tests carried out indicate consistency and uniformity of important product quality characteristics and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the data provided the quality of this medicinal product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

The goal of the nonclinical studies was to support the registration of ponatinib for the proposed indication.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Ponatinib was designed with specific features to gain activity against both native and mutant forms of BCR-ABL, including the T315I gatekeeper mutant. Ponatinib's design includes a carbon-carbon triple-bond functionality to overcome gatekeeper residue steric hindrance as well as optimised binding elements that lead to extensive contacts with the ABL kinase domain, rendering binding less susceptible to disruption by amino acid mutation.

In vitro and *in vivo* studies were conducted to examine the activity of ponatinib in BCR-ABL-driven models of CML. Many of these studies used Ba/F3 cell lines, which were engineered to be dependent on native or mutant BCR-ABL for survival, to examine the potency as well as the mechanism of action of ponatinib. In several of these studies imatinib, nilotinib and/or dasatinib were also examined for comparison.

A broad *in vitro* screen was conducted to understand the kinase selectivity profile of ponatinib. Two sequential screens were performed. First, a broad panel of 235 protein kinases, which included 222 unique human kinases and an additional 13 mutant variants, was assayed using a single ponatinib concentration of 1 μM. In this screen, 56 of 235 kinases demonstrated ≥90% inhibition of kinase activity. A secondary screen was then performed on a panel of 108 kinases, which included enzymes that were strongly inhibited in the first round, to identify IC50 values.

Table 01: *In vitro* Inhibitory Profile of Ponatinib Against 108 Kinases

IC50 ≤2 nM		IC50 ≤20 nM		IC50 ≤200 nM		IC50 >200 nM	
Kinase	**IC50 (nM)**	**Kinase**	**IC50 (nM)**	**Kinase**	**IC50 (nM)**	**Kinase**	**IC50 (nM)**
ABL	0.4	BLK	6.1	BMX/ETK	47	AKT2/PKBb	>1000
ABL (H396P)	0.3	CSK	12.7	BRK	51	ALK	>1000
ABL (M351T)	0.3	DDR2	16.1	EPHA1	143	Aurora A	>1000
ABL (Q252H)	0.4	EPHA2	2.1	ERBB4/HER4	176	Aurora B	543
ABL (T315I)	2.0	EPHA3	6.7	JAK1	32	Aurora C	>1000
ABL (Y253F)	0.3	EPHA7	8.5	JAK2	169	AXL	>1000
ABL2/ARG	0.8	EPHA8	2.5	JAK3	91	BTK	849
EPHA4	1.1	EPHB4	10.2	KIT (D816V)	152	BTK(E41K)	>1000
EPHA5	0.7	FGFR1	2.2	KIT (V654A)	78	CDK2/cyclin E	>1000
EPHB1	1.2	FGFR1 (V561M)	7.3	P38b	173	CTK/MATK/HYL	>1000
EPHB2/HEK5	0.6	FGFR3	18.2	P70S6K	94	EGFR	>1000
EPHB3	1.1	FGFR4	7.7	PYK2/FAK2	35	EGFR (L858R/T790M)	>1000
FGFR2	1.6	FLT1/VEGFR1	3.7	TYK2	177		
FGFR2 (N549H)	0.4	FLT3	12.6			EGFR (L858R)	211
FGR	0.5	FLT4	2.3			EGFR (L861Q)	536
FRK/PTK5	1.3	FMS	8.6			EGFR (T790M)	>1000
FYN	0.4	KDR/VEGFR2	2.9			ERBB2/HER2	>1000
HCK	0.1	KIT	12.5			FAK/PTK2	>1000
KIT (V560G)	0.4	KIT (D816H)	16.0			FER	560
LCK	0.3	P38a	9.8			FES/ FPS	768
LYN	0.2	PDGFRα (D842V)	15.6			FLT3 (D835Y)	948
LYNB	0.2	PDGFRα (T674I)	3.0			IGF1R	>1000
PDGFRα	1.1	PDGFRβ	7.7			IR	>1000
PDGFRα (V561D)	0.8	RAF/RAF1	13.7			IRR/INSRR	>1000
RET	0.2	RET (V804L)	3.7			ITK	>1000
RET (V804M)	1.4	SRC	5.4			MER	406
Yes	0.9	TIE2	14.3			MET	>1000
		TRKA/NTRK1	11.4			mTOR	>1000
		TRKB/NTRK2	15.1			MUSK	694
		TRKC/NTRK3	13.2			PKA	613
						PKCtheta	>1000
						RON/MST1R	>1000
						ROS	>1000
						SRC (T341M)	>1000
						SYK	>1000
						TEC	>1000
						TYK1/LTK	>1000
						TYRO3/SKY	>1000
						ZAP70	>1000

Source: ARIAD Report ARP280

Ponatinib potently inhibits the kinase activity of native ABL (0.4 nM IC50) and has activity against native BCR-ABL in a cellular assay (0.5 nM IC50). Ponatinib also potently inhibits the kinase activity of T315I ABL (IC50-2.0 nM). In cellular assays, ponatinib was able to potently inhibit the activity of all 14 BCR-ABL mutants tested, including T315I, that cause resistance to dasatinib, nilotinib, and/or imatinib.

Of the BCR-ABL mutants tested, T315I, E255K and E255V were inhibited the least, with IC50 values of 11, 14 and 36 nM, respectively. In a cell-based accelerated mutagenesis assay, no mutation in BCR-ABL was detected that could confer resistance to 40 nM ponatinib. Oral administration of ponatinib inhibited BCR-ABL signalling, induced tumour shrinkage and prolonged survival in mice bearing tumours expressing native or T315I mutant BCR-ABL. These preclinical studies support the characterisation of ponatinib as a potent pan BCR-ABL inhibitor.

Table 02: Effect of Ponatinib, Imatinib, Nilotinib, and Dasatinib on Viability of Ba/F3 Cells Dependent on Native or 14 Mutant Variants of BCR-ABL

Ba/F3 Cell Viability Assay IC_{50} (nM)				
BCR-ABL	**Ponatinib[1]**	**Imatinib[2]**	**Nilotinib[2]**	**Dasatinib[2]**
Native	0.5	260	13	0.8
M244V	2.2	2000	38	1.3
G250E	4.1	1350	48	1.8
Q252H	2.2	1325	70	3.4
Y253F	2.8	3475	125	1.4
Y253H	6.2	>6400	450	1.3
E255K	14	5200	200	5.6
E255V	36	>6400	430	11
T315A	1.6	971	61	125
T315I	11	>6400	>2000	>200
F317L	1.1	1050	50	7.4
F317V	10	350	nd	53
M351T	1.5	880	15	1.1
F359V	10	1825	175	2.2
H396P	1.1	850	41	0.6
Parental	1713	>6400	>2000	>200

1: Report OHSU-001
2: O'Hare T. et al (2005) *Cancer Res*. 65: 4500-4505. O'Hare T. et al (2007) *Blood*. 110: 2242-2249.
nd=not determined

Table 03: Effect of Ponatinib, Imatinib, Nilotinib, and Dasatinib, Tested in Parallel, on Viability of Ba/F3 Cells Dependent on Native or 5 Mutant Variants of BCR-ABL

Ba/F3 Cell Viability Assay IC_{50} (nM)				
BCR-ABL	**Ponatinib**	**Imatinib**	**Nilotinib**	**Dasatinib**
Native	0.8	462	21	0.9
Y253F	0.9	3111	66	0.6
E255K	3.2	3731	106	1.5
T315I	8	>10000	>10000	>10000
M351T	1.0	1429	13	0.9
H396P	0.6	996	20	0.4
Parental	1126	>10,000	>10,000	>10,000

Ponatinib also inhibits the activity of other clinically relevant kinases with IC50 values <20 nM and has demonstrated cellular activity against RET, FLT3, and KIT and members of the FGFR, VEGFR and PDGFR families of kinases.

Serum protein binding did not adversely affect the activity of ponatinib. The potency with which ponatinib inhibited the viability of cells expressing T315I mutant BCR-ABL was similar under normal cell culture conditions (8 nM IC_{50}) and in the presence of physiologically-relevant levels of human serum albumin (14 nM IC_{50}).

AP24600, a major metabolite of ponatinib in human plasma, had no effect on the viability of cells expressing native or T315I mutant BCR-ABL (IC_{50} >10,000 nM). AP24567, a minor metabolite of ponatinib in human plasma, inhibited viability of cells expressing native or T315I mutant BCR-ABL with approximately 4-fold reduced potency compared to ponatinib.

In Ba/F3 cells expressing native or T315I mutant BCR-ABL ponatinib induced apoptosis with a half-maximal concentration of 2–57 nM and inhibited phosphorylation of BCR-ABL with an IC_{50} of 25-78 nM. Nilotinib and dasatinib induced apoptosis and inhibited phosphorylation of BCR-ABL in cells expressing native but not T315I mutant BCR-ABL.

Additional studies demonstrated that ponatinib potently inhibited the viability of three BCR-ABL-positive cell lines, but not three BCR-ABL-negative cell lines, derived from leukaemia patients. In one of these BCR-ABL-positive cell lines, K562 cells, ponatinib was also shown to potently induce apoptosis and inhibit BCR-ABL phosphorylation.

To determine whether any single mutation in the kinase domain of BCR-ABL could confer resistance to ponatinib, 3 accelerated mutagenesis studies were performed with ponatinib. In cells exposed to 10 nM ponatinib, limited outgrowth was observed, with a variety of mutations detected at low frequency. In cells exposed to 20 nM ponatinib, outgrowth was sharply curtailed, with only 2 mutations, E255V and T315I, persisting. At 40 nM ponatinib, complete suppression of *in vitro* resistance was observed in all 3 studies. Fourty (40) nM ponatinib was shown to inhibit viability of Ba/F3 cells expressing native BCR-ABL and all 14 mutants tested and 40 nM ponatinib was shown to suppress emergence of any single mutant BCR-ABL clone in 3 separate studies. These results led to the hypothesis that in patients with BCR-ABL-positive disease, trough concentrations of ponatinib greater than 40 nM (21 ng/mL) should result in clinical benefit.

Two types of mouse model systems were used to characterise the *in vivo* activity of ponatinib against native and T315I mutant BCR-ABL. In a survival model in which mice were injected intravenously with Ba/F3 cells that express native BCR-ABL, and in a separate study with Ba/F3 cells expressing T315I mutant BCR-ABL. treatment with ponatinib prolonged survival time in a dose-dependent manner.

In a xenograft model in which mice were injected subcutaneously with K562 cells, which express native BCR-ABL, treatment with ponatinib inhibited tumour growth in a dose-dependent manner. Daily oral dosing with 1 mg/kg ponatinib for 18 days suppressed tumour growth significantly. Daily oral dosing at 2.5, 5, or 10 mg/kg caused tumour regression in all mice. During an 8 week observation period after the last dose, tumour regression was maintained in all mice. Inhibition of BCR-ABL phosphorylation was observed in tumours from mice dosed with ponatinib.

In a xenograft model in which mice were injected subcutaneously with Ba/F3 cells that express T315I mutant BCR-ABL, treatment with ponatinib inhibited tumour growth in a dose-dependent manner. Daily oral dosing at 2.5 and 5 mg/kg for 19 days suppressed tumour growth though it was not statistically significant. Daily oral dosing at 10 and 30 mg/kg caused statistically significant tumour growth inhibition and stasis, respectively. Daily oral dosing at 50 mg/kg caused statistically significant tumour regression. Inhibition of T315I mutant BCR-ABL phosphorylation was observed in tumours from mice dosed with ponatinib.

Secondary pharmacodynamic studies

In vitro, ponatinib inhibited the viability of the FLT3-ITD-positive leukemic cell line, MV-4-11, with an IC50 of 2 nM. In a xenograft model in which mice were injected subcutaneously with MV-4-11 cells, ponatinib inhibited tumour growth in a dose-dependent manner. Dosing at 2.5 mg/kg/day p.o. suppressed tumour growth and dosing at 5 and 10 mg/kg caused significant tumour regression. Inhibition of FLT3-ITD phosphorylation occurred in tumours from mice dosed with ponatinib.

In Ba/F3 cells engineered to express activated FGFR1-4, ponatinib potently inhibited FGFR-mediated signalling and viability with IC_{50}s <40 nM. In a panel of 14 cancer cell lines containing FGFRs dysregulated by a variety of mechanisms, ponatinib inhibited FGFR-mediated signalling with IC_{50}s <40 nM and inhibited cell growth with half maximal concentrations of 7 to 181 nM. Daily oral dosing of ponatinib (10 to 30 mg/kg) to mice reduced tumour growth and inhibited signalling in all 3 FGFR-driven models examined.

In a cell line containing an activating mutation in KIT (N822K), ponatinib inhibited KIT phosphorylation and viability. In a cell line containing an activated PDGFRα (FIP1L1-PDGFRα fusion) ponatinib inhibited PDGFRα phosphorylation and viability. In Ba/F3 cells engineered to express activated RET, ponatinib potently inhibited RET phosphorylation and viability.

These studies indicate that ponatinib is an inhibitor of activated KIT, PDGFRα and RET in cellular models and FLT3 and FGFRs in cellular and *in vivo* models.

Safety pharmacology programme

The programme was carried out to determine the potential effects of ponatinib on CNS, CVS, pulmonary, renal and gastrointestinal systems.

Under the experimental conditions, ponatinib had no clinically relevant effects on the CNS or pulmonary function. Ponatinib at 3, 10, and 30 mg/kg produced increases in urine output and electrolyte excretions without affecting pH or electrolyte concentrations. Ponatinib at 3, 10, and 30 mg/kg did not affect gastrointestinal motility in rats but did cause a non-dose dependent decrease in gastric emptying.

Ponatinib inhibited the hERG current with an IC50 of 2330 nM however this finding may not be clinically significant since this IC50 is well above therapeutic plasma concentration of ponatinib in the clinical setting. An increase in the QTc interval occurred in 1/4 telemetered dogs at an oral dose of 10 mg/kg. However, the relationship to treatment is uncertain based on the short duration at early time points when systemic exposure to the drug was considered submaximal. The QTc interval for this animal returned to baseline prior to expected maximal systemic exposure and remained at baseline for the remainder of a 24 hour observation period. Whilst there may be no unequivocal evidence of QTc interval prolongation, the data shows that the exposure in the dog cardiovascular safety pharmacology was below clinical exposure.

Pharmacodynamic drug interactions

Pharmacodynamic drug interactions have been addressed during the clinical development which is considered acceptable by the CHMP.

2.3.3. Pharmacokinetics

The ADME of ponatinib have been studied in mice (CD-1), rats (Sprague Dawley and Long-Evans), dogs (Beagle), monkeys (*Cynomolgus*) and humans after oral (p.o) and/or intravenous (i.v) administration. Only one of the pharmacokinetic studies was conducted in compliance with GLP. The single dose non-GLP studies were conducted in the discovery phase. They were stated to have been conducted to defined

protocols and GLP-like procedures were followed, hence there was no impact on the validity of these studies. Later in development GLP-compliant studies with complementary pharmacokinetics were conducted.

Absorption

Following oral administration ponatinib was readily absorbed in the mouse but more slowly in the monkey (t_{max} 4h) and rat (t_{max} 6h). The oral bioavailability in the two main test species was 54% in the rat and 26% in the monkey. The terminal half-life of ponatinib in plasma after an IV dose was 9.7 h in the rat and 5.3h in the monkey. The blood clearance was low in the monkey but moderate in the rat.

Distribution

Distribution was investigated in male rats, both the albino Long Evans rat and pigmented Sprague Dawley rat. The distribution of drug-derived radioactivity in pigmented rats was generally similar to that in albino rats. Tissue concentrations in the pigmented uveal tract of the eye of the LE rats (C_{max} of 86.632 µg equiv/g at 96 h) were higher than that in the same tissues of albino rats (C_{max} of 2.099 µg equiv/g at 24 h), suggesting binding of drug-derived radioactivity with melanin. According to the published literature it appears not to be of toxicological significance.

Ponatinib was highly bound to plasma proteins. The extent of protein binding (% bound) was nearly constant across the range of 100 to 3000 ng/mL in all species tested. The mean percent protein binding of ponatinib in all species was in the range 99.92-99.99.

Ponatinib was equally distributed into RBCs and plasma, and did not show preferential partitioning into red blood cells in mouse, rat, monkey, or human blood. Drug derived radioactivity was found in the brain, the T_{max} being 48 hours.

Ponatinib is either a non-substrate or a very weak substrate of P-gp and BCRP and not a substrate of OATP1B1, OATP1B3 and OCT1. Ponatinib is not an inhibitor of transporters OATP1B1, OATP1B3, OCT1, OAT1, OAT3, and OCT2. However, ponatinib is an inhibitor of P-gp, BCRP and BSEP. Inhibition is seen for Pgp and BCRP *in vitro* in the clinical dose range.

Metabolism

The major metabolic pathways of ponatinib in microsomes and hepatocytes were N-demethylation and hydroxylation. *In vitro*, ponatinib was mostly metabolised by CYP3A4 and to a lesser extent by CYP2D6, CYP2C8 and CYP3A5. All *in vitro* metabolites of ponatinib in human liver microsomes/hepatocytes were also observed either in rat or monkey microsomes/hepatocytes.

In vivo, ponatinib was hydrolysed by non-specific esterases or amidases at the amide bond to an acid and aniline. AP24600 was the major metabolite in rat and human plasma but was a trace level metabolite in monkey plasma. In rat, monkey and human plasma, the amide hydrolysis metabolite AP24600 was 263%, < 1% and 58.4% of the ponatinib levels. In rats, the metabolism of ponatinib was mainly to the N-desmethyl metabolite AP24567, which was excreted in faeces, and AP24600 (and its downstream metabolites) which was excreted in urine. In monkey faeces drug-related radioactivity was present mostly as the parent compound or as N-desmethyl ponatinib (M42), hydroxy ponatinib (M31), a double lactam at piperazine moiety (M35) and N-oxide ponatinib (M36). In human faeces, ponatinib accounted for 23.7% of the radioactivity and there was extensive metabolism of ponatinib. Other metabolites identified in human faeces were hydroxy ponatinib, N-desmethyl ponatinib, and several minor metabolites resulting from two or more modifications.

Hydrolytic cleavage of the central amide would yield aniline and the carboxylic acid metabolite: AP24600. The negative results in the *in vivo* micronucleus study are reassuring. On the other hand, there is a

concern that in the *in vitro* tests the appropriate metabolic system to generate the aniline was not used. However, in view of the proposed therapeutic indication and patient population (with advanced cancer) it is considered that further studies are not warranted

DDIs due to CYP inhibition by the metabolite AP24600 are unlikely since the IC_{50} for the inhibition of each of the seven CYPs by AP24600 were all >100 µM. Ponatinib is mostly metabolised by CYP3A4 and esterases. Consequently inhibition of ponatinib metabolism by inhibitors of CYP3A4 might lead to increased exposure to ponatinib whilst induction of CYP3A4 by co-administered drugs might lead to decreased exposure to ponatinib. Ponatinib is metabolized by esterases (or peptidases) to AP24600. Since esterases are ubiquitous, inhibition of esterases leading to increased plasma levels of ponatinib is unlikely.

Excretion

Following an oral dose, ponatinib was mainly excreted in faeces (82- 88%) with 2-10% of the dose recovered in the urine of rats, monkeys, and humans. Overall, ponatinib was eliminated predominantly by metabolism.

2.3.4. Toxicology

Single dose toxicity

Table 04: Single dose toxicity studies:

Type of Study	Species/Strain	Study Duration	Doses (mg/kg)	No. of Animals (Per sex/group)	Study or Report Number
Single dose toxicity	Mouse/CD-1	Single dose	0, 50, 150, 450	Main Study: 10 TK: 24	QAA00123
	Rat/Sprague Dawley	Single dose	0, 10, 30, 100	Main Study: 10 TK: 8	QAA00120
	Monkey/Cynomolgus	Single dose	0, 5, 15, 45	Main Study: 2	QAA00124

In the single dose toxicity studies, in all three species (mouse, rat, monkey) rough hair and dry flaky skin was a common observation.

Repeat dose toxicity

Table 05: Repeat-dose toxicity studies:

Study ID Species/Sex/ Duration/ Number/Group	Dose (mg/kg/ day)	Major findings
QAA00122 **Rat** **28 days** with 28 days recovery 10+5M/10+5F	0 1.5 3 6	Seven (2 males, 5 females) of the 30 animals at 6 mg/kg/day in the toxicology portion of the study were found dead/sacrificed in moribund condition between dose Days 5 and 9. Because of poor health, dosing of animals in this high dose group was stopped. Three (1 male, 2 females) of 30 animals at 3 mg/kg/day in the toxicology portion of the study were found dead/sacrificed in moribund condition between Days 9 and 13. One animal (a male) of 30 animals at 1.5 mg/kg/day in the toxicology portion of the study was found dead on Day 28. 6 mg/kg: Hyperplasia of bone marrow. Minimal to marked necrosis of thymus. Sporadic necrosis of the glandular and non-glandular mucosa of the stomach. ≥3mg/kg: rough hair coats; inappetance; thinness; lethargy; hunched posture; cold skin; dry, red material (porphyrin staining) on the eyes, nose, face, and forepaws; scant feces; urine staining; dark yellow urine; eye squint; and labored breathing. Dry, flaky skin of forepaws. Reduced body weight gain and food consumption. Hyperplasia of epiphyseal plate of the femur. ≥1.5 mg/kg: Slight increases in neutrophils, monocytes and eosinophils and decreases in lymphocytes; most pronounced in 3 and 6 mg/kg groups.

		Transient and minor increases in ALT, AST, BUN, glucose and triglycerides. Slight decrease in thyroid hormone T3. With the exception on lower body weight gain in males at 3 mg/kg, all findings were reversible.
QAA00193 **Rat** **6 months** with 2 months recovery 15+10M/ 15+10F	0 0.25 0.75 2	Mortality: 2 mg/kg: 20/68 animals, 0.75 mg/kg: 3/68 animals. 2 mg/kg: Incease in blood urea nitrogen and creatinine, decreases in albumin, globulin and total protein. Increase in urine protein, correlated to increased incidence of chronic progressive nephropathy. Lymphoid depletion in thymus. ≥0.75 mg/kg: Reduced body weight and food consumption. Increases in neutrophil, monocyte and eosinophil counts. Increase in fibrogen. Inflammation in preputial and clitoral glands. Reduced number of chnodrocytes along the physis in femur. After recovery period, changes in femur at ≥0.75 mg/kg and kidney at 2 mg/kg still present.
QAA00121 **Cynomolgus** **28 days** with 28 days recovery 3+2M/3+2F	0 1 2.5 5	Mortality: 5 mg/kg: Three animals (2M, 1F) euthanized in moribound condition during study (days 19, 21 and 22). 5 mg/kg: Dry flaky skin, mild to marked skin erythema at a large number of anatomical sites. Ocular discharge. Decreased thyroid hormone T3 levels and increased T4 levels. Pancreas diffusely thickened due to either diffuse fibrosis or insterstitial oedema. Acinar cell necrosis or atrophy in pancreas. All early descendants had lymphoid depletion in thymus. Degeneration of germ cell epithelium of testes, decrease numbers of spermatids. Increased follicular atresia in ovaries and atrophy of the uterine endometrium follicles. ≥2.5 mg/kg: Pancreas: Acinar cell necrosis, atrophy or regeneration. Lymphoid depletion in thymus, spleen , lymph nodes and gut associated lymphoid tissue. Granulamotous inflammation of the lung. ≥1 mg/kg: Dose-dependent decrease in body weight and/or body weight gain. Lower food consumption. Systolic heart murmurs in all dose groups (LD 1M, MD 1F, HD 1M+1F). Increase excretion of urinary protein, no microscopic correlates. At the end of recovery period, atrophy of thyroid gland in one male at 5 mg/kg, increased urinary protein at all doses. No microorganisms or evidence for infectious agents were apparent microscopically.
QAA00194 **Cynomolgus** **6 months** with 2 months recovery 4+2M/4+2F	0 0.25 0.75 2	The only noteworthy ponatinib related observations were reversible increases in serum ALT and AST levels. The low degree of toxicity observed at the high dose was likely due to lower than expected exposure levels.

In the rat, histopathological changes in the stomach including hyperkeratosis and necrosis occurred at the top dose of 6mg/kg in the 28-day study, but were absent in the 6-month study. However, the 6-month study was conducted at lower dose levels (top dose 2mg/kg/day at which the multiple of human steady state exposure at the 45mg clinical dose was 1.0) than the 28-day study (top dose 6mg/kg/day at which the exposure multiple was 2.1). These findings were reversible upon cessation of treatment. These findings were not reported in the monkey studies.

In the single dose toxicity study in the monkey on Day 13 post-dose there were systolic heart murmurs (Grade II/VI) in 1/2 males at 45 mg/kg and 1/2 females at 5 mg/kg. These murmurs were not detected during the pre-study physical examination. Heart murmurs were also noted near the end of the 28-day repeat dose toxicity study in surviving animals as follows: one male at 1 mg/kg/day (a low Grade I/VI), one female at 2.5 mg/kg/day (Grade III/VI), one male at 5 mg/kg/day (Grade II/VI) and one female at 5 mg/kg/day (Grade I/VI, intermittent). These findings were reversible during a 28-day non-treatment recovery period. No murmurs were detected during the pre-study physical examinations. No macroscopic or microscopic correlates were noted in the hearts of these animals, including examination of the aortic and other valves. Also they were not reported in the 6 month monkey toxicity study but dose levels were low and the multiples of human steady state exposure were 0.02, 0.82 and 0.46 at 0.25mg/kg, 0.75mg/kg and 2mg/kg (top dose) respectively i.e. below clinical exposure levels.

Inflammatory changes accompanied by increases in neutrophils, monocytes, eosinophils and fibrinogen levels were found in the preputial and clitoral glands in the rat 6-month study. These effects were reversible upon cessation of treatment.

In the monkey 28-day study granulomatous inflammation involving the lungs was present in 1/3 females at 2.5 mg/kg/day and in 2/2 males and 1/3 females at 5 mg/kg/day at the end of the dosing phase. This lesion was characterised by mild to moderate, multifocal aggregates of alveolar macrophages, lymphocytes, and multinucleated syncitial cells within alveolar spaces, occasionally within alveolar spaces off of respiratory bronchioles. It was not reported in the subsequent 6-month study.

Genotoxicity

Table 06: Genotoxic effects of ponatinib

Type of test/study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results Positive/negative/equivocal**
Gene mutations in bacteria 6843-152 GLP	Salmonella and E coli strains	10-5000 µg/plate +/- S9	Negative, reduced growth at ≥333 µg/plate for salmonella strains and at ≥3330 µg/plate for E coli strain
Chromosomal aberrations in mammalian cells 6843-153 GLP	Human peripheral lymphocytes	- 3 µg/ml +/- S9	Negative, greater than 50% cytotoxicity at ≥3 µg/ml and higher doses not analysed for chromosomal aberrations
Chromosomal aberrations *in vivo* 6843-154 GLP	Mouse, micronuclei in bone marrow	125, 500, 1000, 2000 mg/kg single dose, sampling at 24 and 48 h post dose (vehicle and 1000 mg/kg only)	Negative, 100% mortality in 2000 mg/day; these mice were harvested at 21h.

Carcinogenicity

No carcinogenicity studies were submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

Segment I studies are not required according to the EMEA/CHMP/ICH/646107/2008 S9 guideline for medicinal products for the treatment of patients with advanced cancer.

Toxicokinetic data

The recommended daily dose of ponatinib in patients is 45 mg/day. Because of the relatively high sensitivities of the animal species to the toxic effects of ponatinib, a margin of safety either could not be established or was low with respect to the repeat dose toxicity studies relative to the exposure levels obtained in humans at the human oral dose of 45 mg/day (see table 7)

Table 07: Multiples of Human Exposure in Toxicology Studies

Species	Dose (mg/kg)	Single (s) or multiple Doses	Multiples of Human Steady State Exposure at 45 mg clinical dose
Mouse	450	single	47
	1000[a]	single	--
Rat	10	single	5.5
	30	single	18.3
	100	single	65.7
Monkey	5	single	0.7
	15	single	9.1
	45	single	34.6
Rat	1.5	Multiple, 28 days	0.6
	3	Multiple, 28 days	1.1
	6	Multiple, 28 days	2.1
	0.25	Multiple, 180 days	0.07
	0.75	Multiple, 180 days	0.27
	2	Multiple, 180 days	1.0
Monkey	1	Multiple, 28 days	0.09
	2.5	Multiple, 28 days	1.1
	5	Multiple, 28 days	4.4
	0.25	Multiple, 180 days	0.02
	0.75	Multiple, 180 days	0.82
	2	Multiple, 180 days	0.46

a Toxicokinetics not included in study.

Local Tolerance

The local tolerance of ponatinib has been evaluated within the repeat-dose toxicity studies.

Other toxicity studies

In a phototoxicity study, there was no evidence of cutaneous phototoxicity. Low level phototoxic reactions were observed in the form of lenticular epithelial hyperplasia at 5 mg/kg, and in the form of corneal oedema and inflammatory changes, and lenticular epithelial hyperplasia at 10 mg/kg.

2.3.5. Ecotoxicity/environmental risk assessment

The applicant submitted an environmental risk assessment on the active ingredient ponatinib. The ERA included a Phase I assessment. The log K_{ow} was not determined experimentally as stated in the CHMP Q&A on environmental risk assessment.

Table 08: Summary of main study results

Substance (INN/Invented Name): Ponatinib/Iclusig			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}		logP>4.5	Potential PBT Y
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		
	BCF	Not determined	

Persistence	DT50 or ready biodegradability	Not determined			
Toxicity	NOEC or CMR	Not determined			
PBT-statement :	The compound is considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.00405	µg/L			> 0.01 threshold N
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Not applicable					
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Not applicable					

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following point to be addressed:

The Applicant will conduct appropriate studies to assess the environmental risk and submit the results by March 2014.

2.3.6. Discussion on non-clinical aspects

Ponatinib was shown to inhibit viability of Ba/F3 cells expressing native BCR-ABL and all 14 clinically relevant mutants tested, including T315I, with IC50 values of 0.5 to 36 nM. Serum protein binding did not adversely affect the activity of ponatinib.

Preclinical studies have shown that certain compound mutations in BCR-ABL, defined as two or more mutations in the same BCR-ABL allele, can confer resistance to ponatinib; the T315I/E255V compound mutant may confer clinically relevant resistance. As shown in vitro, activation of the PI3K/AKT/mTOR and STAT3 pathways may potentially constitute BCR-ABL-independent mechanisms of resistance to ponatinib. No information on the effect of p53 mutation status or function on the efficacy of ponatinib is available.

Ponatinib was highly bound to plasma proteins. Ponatinib is either a non-substrate or a very weak substrate of P-gp and BCRP and not a substrate of OATP1B1, OATP1B3 and OCT1. Ponatinib is not an inhibitor of transporters OATP1B1, OATP1B3, OCT1, OAT1, OAT3, and OCT2. However, ponatinib is an inhibitor of P-gp, BCRP and BSEP.

The major metabolic pathways of ponatinib in microsomes and hepatocytes were N-demethylation and hydroxylation. In vivo, ponatinib was hydrolysed by non-specific esterases or amidases at the amide bond to an acid and aniline. AP24600 was the major metabolite in rat and human plasma. Following an oral dose, ponatinib was mainly excreted in faeces (82- 88%).

Ponatinib has been evaluated in safety pharmacology, repeat-dose toxicity, genotoxicity, reproductive toxicity, and phototoxicity studies.

Dose-limiting toxicity was expressed as mortality and occurred at exposures below clinical exposure. The cause for mortality was not clearly established.

Cynomolgus monkeys were selected as the non-rodent species for toxicology testing.

Dry flaky skin, rough coats and thinning fur was also a common observation in the repeated dose toxicology studies at clinically relevant exposure levels.

Depletion of lymphoid organs was observed in repeat-dose toxicity studies in rats and cynomolgus monkeys. The effects were shown to be reversible after withdrawal of the treatment. It is unknown whether ponatinib causes lymphoid depletion in humans. Decreases in peripheral lymphocyte counts (20.8% grade 3 or 4) were observed in the clinical studies, however, the relationship to lymphoid depletion is unclear.

Approved BCR-ABL inhibitors are associated with congestive failure/left ventricular dysfunction (imatinib) and conduction abnormalities (QT prolongation) (dasatinib; nilotinib). A thorough QT/QTc study has not been conducted and the effect of ponatinib on QT prolongation cannot be ruled out (see section 4.4 of the SmPC).

Hyper-/hypoplastic changes of the chondrocytes in the physis were noted in repeat-dose toxicity studies in rats. The effect was reversible upon cessation of treatment in the 28-day study but not in the 6 month study. These findings may be species specific since they were not reported in either monkey studies.

While mild-moderate visual disturbances were occasionally reported in clinical trials, there were no reports of ocular phototoxicity. In a study in rats, diffuse corneal oedema with neutrophilic cell infiltration, and hyperplastic changes in the lenticular epithelium suggestive of a mild phototoxic reaction were observed in animals treated with 5 and 10 mg/kg ponatinib (see section 5.3 of the SmPC).

In cynomolgus monkeys, systolic heart murmurs with no macroscopic or microscopic correlates were noted in individual animals in the toxicity studies. The clinical relevance of this finding is unknown. Nevertheless, it has been reflected in section 5.3 of the SmPC.

The pancreas was identified as a target organ of toxicity in the 28 day toxicity study in monkeys. This observation correlated with the identification of pancreatitis as the dose limiting toxicity in the clinical program. Elevations in pancreatic enzymes and clinical pancreatitis were observed in humans. Pancreatitis is an identified risk in the RMP.

Thyroid gland follicular atrophy mostly accompanied by a reduction in T3 levels and a tendency toward increased TSH levels were observed in the 4-week repeat-dose toxicity study in cynomolgus monkeys. No noteworthy changes in thyroid hormone have been observed in humans, in particular, decreased serum T3 values were not observed in clinical studies. In addition TSH values were routinely measured in the phase 1 study and clinically relevant levels of increased TSH were not observed.

The histological changes observed in the femur of rats appear to be species specific since histological changes in the femur were not observed in the monkey studies. However, because of emerging concerns of growth delay in children exposed to long term imatinib and possibly other TKIs (Suttorp 2010), the Applicant proposed to monitor growth in children receiving ponatinib.

In the monkey 28-day study, granulomatous inflammation involving the lungs was present at the end of the dosing phase. The cause of the granulomatous inflammation in this study is unknown. The clinical data shows no evidence of pulmonary granulomatous inflammation. The evidence indicates that these findings in the monkey are not of clinical relevance.

Slight increases in liver enzyme levels were observed at clinically relevant or lower exposure levels in the repeat dose toxicology program. However, there were no histological correlates observed upon microscopic examination of liver specimens. Elevated liver enzyme levels (including ALT and AST) were observed in clinical trials. No Hy's law cases were identified in the ponatinib clinical development program. This finding is addressed in the SmPC and in the RMP as an important identified risk.

The administration of ponatinib was associated with transient increase of glucose and triglycerides in the rat. In some monkeys there was an increase in triglycerides but this was not invariably associated with pancreatitis. The clinical data presented did not indicate a clinical relevance of increased glucose or triglycerides in the development of pancreatitis in patients treated with ponatinib.

Ponatinib did not exhibit genotoxic properties when evaluated in the standard *in vitro* and *in vivo* systems.

According to the guideline EMEA/CHMP/ICH/646107/2008 S9, carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer.

Possible ponatinib-related findings in the 28 day repeat-dose toxicity studies in cynomolgus monkey study at 5mg/kg/day included degeneration of germ cell epithelium with decreased number of spermatids in males, and increased ovarian follicular atresia with associated atrophy of endometrial follicles in females. The clinical relevance remains unclear. These issues are addressed in section 5.3 of the SmPC. The Applicant will conduct a formal study in rats to evaluate the effects of ponatinib on male fertility, as reflected in the RMP. Results will be submitted by December 2015.

In rats, embryo-foetal toxicity in the form of post-implantation loss, reduced foetal body weight, and multiple soft tissue and skeletal alterations were observed at maternal toxic dosages. Multiple foetal soft tissue and skeletal alterations were also observed at maternal nontoxic dosages.

In the ERA conducted by the Applicant, the PBT screening was lacking. Whilst the data calculated by the applicant is above the trigger for PBT, it is recommended that a correct experimentally determined log Kow value is provided accompanied by a study report as stated in the CHMP Q&A on environmental risk assessment. When log Kow is above 4.5, a PBT assessment is warranted irrespective of the PECsw. If appropriate, it is recommended to finalise a PBT assessment. The PBT should follow the REACH guidance meaning that a BCF value should be obtained before embarking on animal studies. The 100 ton/yr limit is not considered relevant in this matter. It is recommended that the Applicant submits the relevant results by March 2014.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical studies conducted were adequate to support the marketing authorisation of ponatinib in the treatment of ALL and CML.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

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

- Tabular overview of clinical studies

Protocol Number	Phase	Protocol Title	Patient Population	Dosing	Status
AP24534-07-101	1	A Phase 1 Dose Escalation Trial to Determine the Safety, Tolerability and Maximum Tolerated Dose of Oral AP24534 in Patients with Refractory or Advanced Chronic Myelogenous Leukaemia and other Hematologic Malignancies	Adult patients (≥18 years old) with refractory or advanced chronic myeloid leukaemia (CML) and other hematologic malignancies	Oral once daily administration Dose levels were 2 mg, 4 mg, 8 mg, 15 mg, 30 mg, 45 mg, and 60 mg	Ongoing, N=81 Initiated June 2008 Enrolment completed October 2010
AP24534-11-102	1	An Open-Label, Randomized, Single-Dose, 3-Period Crossover Study to Determine the Effect of a High-Fat Meal and a Low-Fat Meal on the Relative Bioavailability and Pharmacokinetics of a Single Dose of Ponatinib Administered Orally to Healthy Subjects	Healthy subjects (18 to 55 years of age, inclusive), in good health, with BMI of 18.0 to 33.0 kg/m^2 and a minimum weight of 50.0 kg at screening.	Three single, oral doses of 45 mg of ponatinib, given in the fasting state, after a high-fat meal, and after a low-fat meal.	Completed, N=24
AP24534-11-103	1	An Open-Label, Randomized, 2-Period Crossover Study to Evaluate the Potential Pharmacokinetic Interaction between Multiple Doses of Ketoconazole and a Single Dose of Ponatinib Administered Orally to Healthy Subjects.	Healthy subjects (18 to 55 years of age, inclusive), in good health, with BMI of 18.0 to 33.0 kg/m^2 and a minimum weight of 50.0 kg at screening.	Two single, oral doses of 15 mg of ponatinib, once given alone and once co-administered with daily doses of 400 mg of ketoconazole for 5 days.	Completed, N=24
AP24534-11-104	1	A Phase I, Open-Label, Mass Balance Study to Investigate the Absorption, Metabolism and Excretion of [^{14}C]-Ponatinib after a Single Oral Dose in Healthy Male Subjects	Healthy male subjects (19 to 45 years of age, inclusive), in good health, with BMI of 18.0 to 30.0 kg/m^2, and weight of 50.0 to 100.0 kg at screening.	Single, 45 mg oral dose of [^{14}C]ponatinib	Completed, N=6
AP24534-10-201	2	A Pivotal Phase 2 Trial of Ponatinib (AP24534) in Patients with Refractory Chronic Myeloid Leukaemia and Ph+ Acute Lymphoblastic Leukaemia	Adult patients (≥18 years old) with CML in chronic phase (CP), accelerated phase (AP) or blast phase (BP) or with Ph+ acute lymphoblastic leukaemia (ALL) who either: Are resistant or intolerant to either dasatinib or nilotinib Or Have the T315I mutation.	Oral 45 mg once daily	Ongoing, N=449 Initiated September 2010 Enrolment completed October 2011

The phase I dose finding study and the phase II pivotal study were performed in patients. The other 3 phase I studies (food effect study, drug interaction study and mass balance study) were conducted in healthy subjects. Population PK analysis has been performed in patients in the phase I dose finding study. Target effect PD measurements have been performed in the dose finding study by investigating the reduction in phosphorylated CRKL in patients with CML and Ph+ ALL. This clinical data was supplemented by data from 7 *in vitro* studies.

The applicant claimed the approval for the following indication:

Iclusig is indicated in adult patients with chronic phase, advanced phase, or blast phase chronic myeloid leukaemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant or intolerant to prior tyrosine kinase inhibitor therapy.

The final indication following CHMP review of this application is:

Iclusig is indicated in adult patients with

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

2.4.2. Pharmacokinetics

No pharmacologically active metabolites have been described for ponatinib. The major metabolite identified in humans is AP24600, formed by amide hydrolysis of ponatinib. This metabolite was only identified during the mass balance study, and was found in humans, rats, and monkeys (albeit at low levels). CYP3A4/5-mediated metabolism of ponatinib *in vitro* resulted in the formation of both AP24567 and AP24734. AP24567 (N-desmethyl metabolite) was subsequently identified as a metabolite of ponatinib in human plasma, whereas AP24734 was not observed to any significant extent in patient plasma. Plasma levels of AP24567 were approximately 1% to 2% of ponatinib plasma levels in patients.

Absorption

Absolute oral bioavailability of ponatinib in humans has not been determined. Ponatinib HCl is considered a "low solubility" compound due to its insolubility in aqueous solution above pH 2. Combined with high permeability assessed using the Caco-2 cell transport, ponatinib is categorised as a BCS Class II compound. Under fasting conditions, maximum ponatinib blood concentrations in patients with hematologic malignancies generally occurred 4 to 6 hours following oral administration of ponatinib. Following single dose administration, as well as under steady-state conditions, ponatinib plasma exposures (C_{max} and AUC) increased in a manner approximately proportional with increasing dose.

The influence of a high-fat meal and a low-fat meal on the relative bioavailability and the pharmacokinetics of a single dose of ponatinib were studied in healthy volunteers, and this showed no effect.

Distribution

The steady-state apparent volume of distribution (Vd/F) of ponatinib at the recommended 45 mg dose was estimated to be 1101 L.

In vitro binding of ponatinib in human plasma was estimated to be greater than 99%. The blood to plasma partition ratio of ponatinib was 0.96 in human blood. Ponatinib was equally distributed into RBCs and plasma and did not show preferential partitioning into red blood cells.

AP24600, the major metabolite in human and rat plasma, was also highly bound to plasma proteins. The extent of protein binding in human and rat plasma was 94.7% and 93.5 %, respectively.

Elimination

The estimated apparent clearance of ponatinib at steady-state (CLss/F) at the recommended 45 mg dose is 35 L/h (CV=55%, N=20). The terminal elimination half-life of ponatinib at steady state at a daily dose of 45 mg was 22 hours, resulting in a 1.5-fold accumulation of exposures at steady-state.

In the human mass balance study, AP24534-11-104, faecal excretion accounted for elimination of 86.63% of the radioactive dose. Ponatinib was the largest peak in the radiochromatogram accounting for 23.7% of the faecal radioactivity. M31 (20.4%) was identified as hydroxyl ponatinib. Other metabolites M36, M47 and M49 were approximately 2-4% of the total radioactivity. Several, chromatographically not well-resolved, metabolites (33.0 to 37.6 min) together accounted for 17.2% of the faecal radioactivity; and individually each metabolite accounted for 2-3%.

The amount of drug and metabolites eliminated through urine was 5.4% of the dose. The metabolite profile in urine was dominated by AP24600 (M14) and its glucuronides, M15 and M16. These metabolites accounted for 5.6% (M14) 28.1% (M15) and 19.8% (M16). M24 was identified as ponatinib hydroxyl-glucuronide and contributed 5.1% to the urinary profile.

In plasma samples from the ADME study a long terminal half-life of radioactivity of 149 hours is seen, further profiling of these samples is required to determine what is contributing to this long half-life. The Applicant committed to evaluate plasma samples from the human ADME study in order to identify and quantify metabolites of ponatinib. The Final report will be submitted by December 2016.

Dose proportionality and time dependencies

Dose proportionality of ponatinib was investigated in study AP24534-07-101. Ponatinib showed dose proportional increase in Cmax and AUC with dose at steady-state.

In the population PK analysis, clearance was described to increase as a function of ponatinib concentration and time. For a daily dose of 45 mg, a decrease in the steady state concentration by 26% was predicted compared to a situation where no change in clearance was assumed.

As the data in study AP24534-07-101 did not support estimation of terminal elimination rate constant after single-dose administration, assessment of within-study time dependency is not possible based on the submitted data. The Applicant has used between study comparisons to assess the time-dependency in ponatinib exposure (AUC) (see Table 9).

Table 09: Ponatinib between study comparisons for assessment of time-dependency

Dose	Single-dose (SD) AUC0-inf (h*ng/ml)	Steady-state (SS) AUC0-τ (h*ng/ml)	Ratio SS/SD
15 mg	508.1[a]	510.6[c]	1.10
45 mg	1329[b]	1463[c]	1.00

[a] AP24534-11-103 (DDI study) healthy volunteers
[b] AP-24534-11-102 (Food effect) healthy volunteers
[c] AP24534-07-101 (Dose escalation) patients

In the population PK analysis, inter-individual variability (CV%) in CL/F was about 47 % and for V1/F 44%. Intra-individual variability (CV%) in healthy volunteers was approximately 13 % for relative F and 69.5 % higher in patients.

Special populations

Impaired renal function:

The effect of baseline serum creatinine and estimated creatinine clearance (Cockcroft Gault formula) was found to not have a significant effect on ponatinib concentrations. The median (range) baseline serum creatinine of the 128 subjects included was 0.91 ng/dL (0.38 to 2.1 ng/dL) and the median (range) estimated creatinine clearance was 105 mL/min (33.8 to 184 mL/min). Only four of the included patients had an estimated creatinine clearance < 50 mL/min, and no patient < 30 mL/min.

Impaired hepatic function:

Ponatinib has not been formally evaluated in patients with hepatic impairment.

Gender:

Of the total 128 patients or healthy subjects included in the analysis, 90 (70%) were males and 38 (30%) were females. There does not appear to be a gender effect on the pharmacokinetics of ponatinib.

Weight:

Both the effect of weight and body mass index (BMI) on ponatinib pharmacokinetics has been evaluated. The median (range) weight of the total 128 subjects included was 77.4 kg (41.7 to 125 kg). The median (range) BMI of the evaluable population was 27 kg/m^2 (16.3 to 41.1 kg/m^2). BMI but not weight was found to be a statistically significant covariate on apparent volume of distribution of the central compartment (V/F). A person with a BMI level equal to the upper 90th percentile (34 kg/m^2) was predicted to have a 14.5% increased V/F whereas a person with an BMI level equal to the lower 10th percentile (21 kg/m^2), was predicted to have 14.1% lower V/F. The effect of BMI on V/F was however not considered clinically relevant.

Age:

The model used in the PK studies does not suggest a large effect of age on clearance, with an 18% decrease for a subject age 70.

Pharmacokinetic interaction studies

In vitro

Ponatinib was incubated with individual recombinant human CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP3A4/5, and CYP2C9). Ponatinib was stable in the incubations with all enzymes tested, except CYP3A4, CYP3A5, CYP2C8 and CYP2D6. Nearly 55% of ponatinib was metabolised by CYP 3A4/5 at 60 min leading to metabolites AP24567 (30%), AP24734 (24%) and mono-oxy ponatinib (2%). Metabolism of ponatinib by CYP 3A4/5 was qualitatively identical to the metabolism by liver microsomes and hepatocytes. The results from studies where ponatinib metabolism was selectively inhibited by CYP-specific inhibitors and monoclonal antibodies indicate that ponatinib was metabolised mostly by CYP3A4 and to a lesser extent by CYP2D6, CYP2C8 and CYP3A5. Since human metabolism of ponatinib involves CYP3A4/5 isozymes, drug-drug interactions (DDIs) with co-administered CYP3A4/5 inhibitors and inducers are possible. These in vitro data have been followed with a clinical study evaluating the impact of ketonconazole mediated CYP3A4/5 inhibition on single dose ponatinib PK (AP24534-11-103).

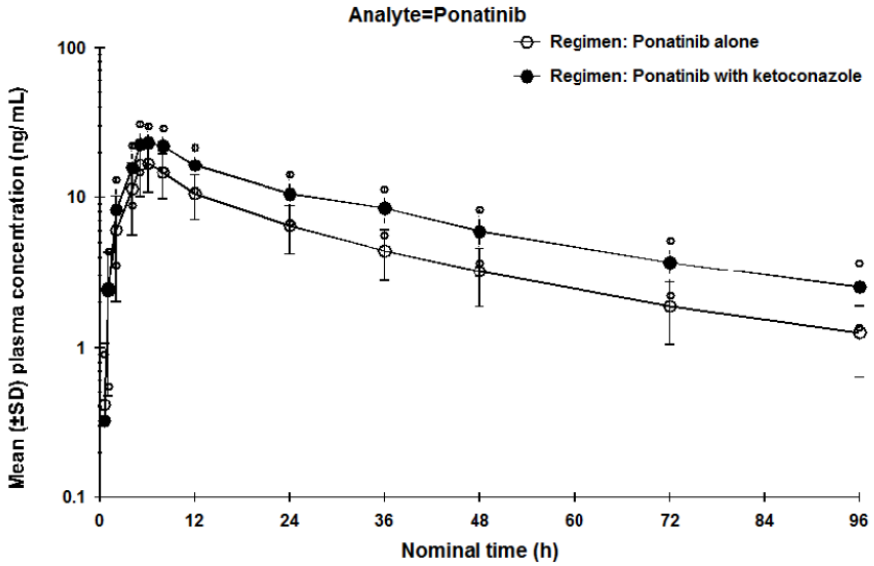
In vitro data showed that ponatinib does not behave either as an inhibitor or an inducer of all major human drug metabolising CYP450 enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4) *(Report ARP267)*. Further, in vitro data using human hepatocytes demonstrated that ponatinib did not alter CYP1A2, CYP2B6, or CYP3A4 enzyme activity or messenger RNA (mRNA) levels or CYP2C9 mRNA levels. It was concluded that ponatinib was not an inhibitor or an inducer of major CYP enzymes and that the potential for CYP enzyme inhibition- or induction-mediated drug interaction by ponatinib is low at the therapeutic dose of 45 mg. Based on these data, no clinical studies evaluating ponatinib effect on CYP probe substrates have been performed.

In vitro data also indicated that ponatinib was a concentration-dependent inhibitor of P-gp and BCRP, with IC50 values of 0.491 µM and 0.013 µM, respectively. Ponatinib also showed weak concentration-dependent inhibition of BSEP that is not expected to be clinically relevant (IC50 of 31.5 µM). Ponatinib was shown not to be an inhibitor of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, or OAT3. Based on these *in vitro* data, ponatinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp or BCRP.

In vivo

One drug interaction study (AP24534-11-103) has been conducted to evaluate the effects of concomitant administration of ketoconazole on the pharmacokinetic (PK) profile of ponatinib following single-dose administration in healthy subjects.

The results showed a 78% and 47% increase in plasma ponatinib AUC0-∞ and Cmax, respectively, without affecting time to achieve maximum plasma concentrations, following co-administration with ketoconazole.



2.4.3. Pharmacodynamics

Mechanism of action

No clinical mechanism of action studies were submitted by the applicant.

Primary and Secondary pharmacology

The pharmacodynamic activity of ponatinib was studied as one of the secondary objectives of the ponatinib phase 1 trial (AP24534-07-101). The activity of ponatinib was studied in CML and Ph+ ALL patients, including patients with T315I mutant BCR-ABL. Pharmacodynamic assessments were performed on 64 of 65 CML and Ph+ ALL patients enrolled in the study by measuring relative levels of phosphorylation of the BCR-ABL substrate CRKL (pCRKL), relative to total CRKL, in peripheral blood mononuclear cells (PBMCs), at baseline and multiple time points throughout the first cycle of ponatinib treatment.

pCRKL, a BCR-ABL adaptor protein, serves as a surrogate of BCR-ABL kinase activity in vivo.

Fourty three (43) of the 61 patients were ultimately considered evaluable for pharmacodynamics assessment.

- No substantial reduction was seen in the 2 evaluable patients in the lowest dose cohort (2 mg).
- A partial reduction of pCRKL (≥25% or ≥50%) was seen in 1 evaluable patient in the 4 mg cohort.
- A reduction of ≥50% was seen in 4/6 (67%) patients receiving the 8 mg dose, with no substantial reduction in 2 patients, both of whom had T315I mutant BCR-ABL.
- At doses ≥15 mg, 32/34 (94%) patients, including 8/10 (80%) patients with T315I, demonstrated a ≥50% reduction of pCRKL. One patient at 15 mg had a reduction of ≥25% to <50% and 1 patient at 45 mg had a reduction of <25%.
- One patient at 15 mg had a reduction of ≥25% to <50% and 1 patient at 45 mg had a reduction of <25%.

Of the 21 non-evaluable patients, 6 patients were lacking either a baseline sample or a sufficient number of post treatment samples for evaluation. An additional 15 patients were considered non-evaluable due to baseline pCRKL levels ≤20%. Notably, in 14 of these patients pCRKL levels were maintained at ≤20% at trough time points. The one exception was a patient who showed a transient elevation of pCRKL levels after an 8-day period off therapy.

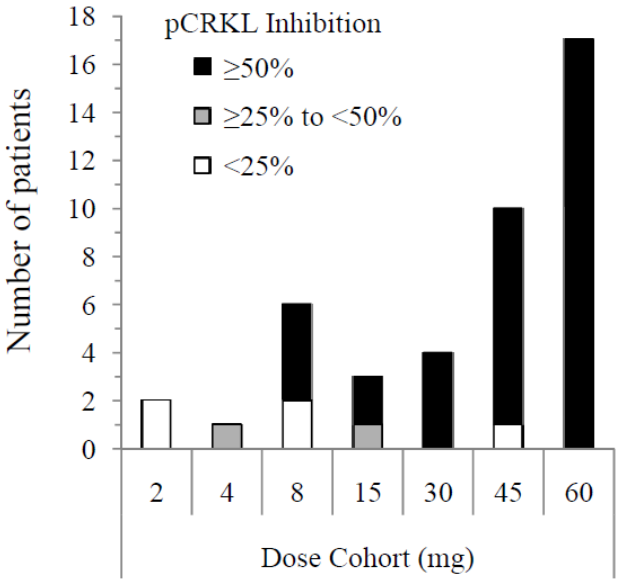


Figure 01: Summary of pharmacodynamics data in Phase 1 clinical trial AP24534-07-101

2.4.4. Discussion on clinical pharmacology

Ponatinib is a TKI targeting a broad range of kinases. Activity against BCR-ABL, RET, FLT3, and KIT and members of the FGFR, VEGFR, and PDGFR families of kinases has been shown in cellular assays. Importantly, also investigated BCR-ABL mutants, including the T315I mutation, are inhibited with IC50s <40 nM; T315I, E255K and E255V were inhibited least potently, with IC50 values of 11, 14 and 36 nM, respectively. Clinical efficacy in T315I+ disease is supported by animal experiments.

In plasma samples from the ADME study a long terminal half-life of radioactivity of 149 hours is seen. The Applicant will evaluate plasma samples from the human ADME study to identify and quantify metabolites of ponatinib. The Final report will be submitted by December 2016.

In order to address missing information regarding time dependency of the pharmacokinetics of ponatinib, the Applicant will update the population PK model with PK data from ongoing clinical trials to address missing information related to. The updated model will be available by March 2016.

The Applicant has conducted a comprehensive package of *in vitro* studies to support inferences regarding the potential impact of co-administration of ponatinib with other drugs.

Ponatinib is metabolised by CYP3A4. Co-administration of a single 15 mg oral dose of Iclusig in the presence of ketoconazole (400 mg daily), a strong CYP3A inhibitor, resulted in modest increases in ponatinib systemic exposure, with ponatinib AUC0-∞ and Cmax values that were 78% and 47% higher, respectively, than those seen when ponatinib was administered alone.

Caution should be exercised with concurrent use of Iclusig and moderate or strong CYP3A inhibitors such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and grapefruit juice.

One *in vivo* drug interaction study was performed to look at the effect of ketoconazole on ponatinib but only a single dose of ketoconazole was given prior to administration of ponatinib in the interaction study. The Applicant has therefore included "Treatment of patients receiving concomitantly CYP3A4 inhibitors" as important missing information in the RMP, pending results of PBPK modelling of the interaction of ponatinib with twice-daily ketoconazole dosing. Results of this modelling experiment are expected to be available by the end of 2013.

The effect of CYP3A inducers on ponatinib pharmacokinetics has not been studied. Based on the role of CYP3A in the metabolism of ponatinib, it is anticipated that strong inducers will decrease ponatinib systemic exposures; however, the magnitude of decrease is unknown. Caution should be exercised with concurrent use of Iclusig and strong CYP3A inducers such as carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, and St. John's Wort.

The aqueous solubility of ponatinib is pH dependent, with higher pH resulting in lower solubility. Medicinal products that elevate the gastric pH (such as proton pump inhibitors, H2 blockers, or antacids) may decrease the solubility of ponatinib and subsequently reduce its bioavailability. Caution should therefore be exercised in case of concurrent treatment. The Applicant will conduct an interaction study with a PPI. At present caution is recommended in section 4.4 of the SmPC with drugs that affect gastric pH, the results of this study should be used to further inform wording in the SmPC.

In vitro, ponatinib is an inhibitor of P-gp and BCRP. Therefore, ponatinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp (e.g., digoxin, dabigatran, colchicine, pravastatin) or BCRP (e.g., methotrexate, rosuvastatin, sulfasalazine) and may increase their therapeutic effect and adverse reactions. Close clinical surveillance is recommended when ponatinib is administered with these medicinal products.

Induction of cytochrome P450 isozymes by ponatinib was added as important missing information in the RMP and the Applicant committed to conduct an induction study in hepatocytes using higher concentrations of ponatinib to allow determination of CYP3A4 induction. The results of this study should be submitted by March 2014. A possible effect of induction of CYP450 isozymes by ponatinib could be a decrease in the exposure to oral contraceptives. To ensure this is not the case, an interaction study between ponatinib and oral contraceptives will be conducted by the Applicant. The Final report will be submitted by December 2016.

On the basis of the results of the observed 5.4% urinary excretion of administered radioactivity, in the human mass balance study, the applicant concluded that renal excretion is not a major route of excretion for ponatinib. Therefore a renal excretion study was not conducted. However, a statement has been included in section 4.4 of the SmPC to advise caution when administering ponatinib in patients with estimated creatinine clearance of <50mL/min, or with end-stage renal disease.

As the hepatic route is a major route of elimination, the presence of moderate to severe hepatic impairment may result in increased plasma ponatinib concentrations. The Applicant will conduct a study in patients with hepatic impairment to address the lack of data in this patient population. The Final report will be submitted by July 2014. Pending the results of this study, treatment with ponatinib should be used with caution in patients with varying degrees of hepatic impairment.

Data is limited regarding the effect of age on ponatinib pharmacokinetics.

There was no clinically significant effect of weight over the weight ranges studied.

Once daily oral dosing of ponatinib to patients resulted in sustained inhibition of BCR-ABL signalling. Maximal activity, including in patients with T315I mutant BCR, was seen at dose levels of 15 mg and above.

2.4.5. Conclusions on clinical pharmacology

Ponatinib is a low solubility, high permeability (BCS class 2) compound. Over the proposed clinical dose range of 15- 45 mg the exposure appears to be linear with a C_{max} of 77 ng/ml (0.1 nM free) following 45 mg. Food does not have a significant effect on the exposure of ponatinib.

Ponatinib is extensively metabolised with the majority of excretion in the faeces. Enzymes responsible for the metabolism are CYPs (3A4, and to a lesser extent CYPs 2C8 and 2D6); and amidase/esterase hydrolysis in the gut. Products of the hydrolytic cleavage are the carboxylic acid which is the major circulating metabolite and the aniline which does not circulate to any great extent but whose elimination has not been fully quantified. Consistent with the involvement of CYP3A4 in the elimination co-administration with ketoconazole results in an interaction (78% increase in AUC).

In *in vitro* studies, ponatinib does not inhibit cytochrome P450's or the drug transporters, OATP1B1, OATP1B3, OCT1, OAT1, OAT3, and OCT2, but it is an inhibitor of Pgp and BCRP with IC50s of 0.491 and 0.013 µM.

2.5. Clinical efficacy

The Applicant submitted two clinical studies relevant to the efficacy of ponatinib in the proposed indications.

2.5.1. Dose response study

This phase 1 study (AP24534-07-101) is ongoing in the United States. Patients were enrolled from 05 June 2008 to 13 October 2010. The data presented includes data up to a cut-off date of 06 January 2012, and summarise observations made for a total of 81 eligible patients who were enrolled and received oral, once daily doses of ponatinib. At the time of analysis (23 March 2012), 33 patients (40.7%) remained on therapy, and median follow-up for all patients was 14.5 (0.4 to 41.0) months, and median follow-up for Ph+ leukaemia patients was 21.1 (0.5 to 41.1) months.

Patients were sequentially assigned to starting dose level cohorts as they enrolled. Dose levels were 2 mg, 4 mg, 8 mg, 15 mg, 30 mg, 45 mg, and 60 mg ponatinib once daily. Over the course of the study, patients were escalated and/or de-escalated (using protocol-defined criteria to manage side effects) to an appropriate dose of ponatinib. The starting dose of ponatinib was 2 mg/day. This dose level was selected on the basis of data obtained from the 28-day oral toxicology studies in rats and monkeys, as well as taking into consideration the prospective clinical trial patient population. The rationale for selecting the starting dose was as follows: an acceptable method for selecting the first dose of nonspecific cytotoxic agents for a first-in-human trial in cancer patients is to begin with a dose that is 1/10 of the lethal dose for 10% of animals (LD10) in mg/m2 in rodents, provided that this dose level is shown to be tolerated in a non-rodent species (*DeGeorge et al, 1998)*. The LD10 of the 28-day regimen in rats was between 1.5 mg/kg (9 mg/m2) and 3 mg/kg (18 mg/m2). Assuming human patients had a BSA of 1.7 m2, the lower BSA equivalent dose for humans was approximately 15 mg. Based on the rule of 1/10 of the LD10 in mg/m2 in rodents, the starting dose in humans would be somewhat higher than 1.5 mg. Therefore, 2 mg/day represented a conservative and acceptable starting dose.

No DLTs were observed in patients in cohorts up to 30 mg (cohort 5). In cohort 6, the next cohort, 60 mg was administered, and 4 DLTs were observed in 11 evaluable patients. The next cohort (cohort 7) was 45 mg, and 1 DLT was observed in 12 DLT-evaluable patients. At this point, the cohort 7 tablet dosage form

was introduced, and 45 mg (cohort 8; no DLTs) and 60 mg (cohort 10; 2 DLTs) cohorts were enrolled. The DLTs observed in the pooled 45 and 60 mg cohorts are summarised in Table 10.

Table 10: Dose escalation and summary of dose-limiting toxicity

Dose (mg/day)	Patients (n)	Patients Evaluable for Dose-limiting Toxicity (n)	Patients With Dose-limiting Toxicities (n)	Dose-Limiting Toxicity Events
2	3	3	0	0
4	6	6	0	0
8	7	6	0	0
15	8	7	0	0
30	7	5	0	0
45	19	18	1	Rash
60	19	16	6	Pancreatic (n=4), fatigue (n=1), elevated ALT (n=1)
Source: Section 14 Table 14.1.1 (patient disposition by cohort), Appendix 16 Listing 16.4.3.1.7 (Investigator-determined DLTs); Appendix 16 Listing 16.4.3.1.12 (Sponsor-determined DLT: Patient 005-0017 at 60 mg/day). Database cutoff date 23 March 2012.				

Pancreatic events were the most commonly occurring DLTs. Four patients treated at 60 mg daily had pancreas-related DLTs during the defined cycle 1 DLT evaluation period; these consisted of grade 3 or 4 increased lipase and/or blood amylase concurrent with clinical evidence of pancreatitis. Two patients treated at 60 mg experienced other DLTs; 1 with grade 3 fatigue; and, 1 with grade 3 ALT and AST increased. At 45 mg, there was 1 DLT of grade 3 maculo-papular rash.

Of the 7 patients with DLTs, 3 continued study participation, 3 discontinued study treatments for reasons other than the DLT they experienced, and 1 discontinued due to the DLT.

In summary, while some patients were able to tolerate 60 mg and remain on study at this dose, the safety data are consistent with 60 mg exceeding the MTD of 45 mg. No DLTs were reported in patients with AML or other hematologic malignancies.

Some evidence of the activity of the lower doses is also available from the results, but the numbers of patients, on doses lower than 45 mg, are small. However, it can be said that there was appreciable activity noted with the lower doses. (see table 11)

Table 11: Ponatinib Phase 1 Study: Response by Starting Dose CP-CML

Response	Response Rate, n (%)					
	Total CP-CML N=43	Cohort 2 4 mg N=3	Cohort 4 15 mg n=7	Cohort 5 30 mg N=5	Cohorts 7&8 45 mg N=14	Cohorts 6&10 60 mg N=14
Cytogenetic						
MCyR	31 (72.1)	2 (66.7)	5 (71.4)	3 (60.0)	13 (92.9)	8 (57.1)
CCyR	28 (65.1)	1 (33.3)	4 (57.1)	3 (60.0)	13 (92.9)	7 (50.0)
PCyR	3 (7.0)	1 (33.3)	1 (14.3)	0	0	1 (7.1)
Molecular						
MMR	19 (44.2)	1 (33.3)	3 (42.9)	1 (20.0)	9 (64.3)	5 (35.7)

2.5.2. Main study

Study AP24534-10-201: A Pivotal Phase 2 Trial of Ponatinib (AP24534) in Patients with Refractory Chronic Myeloid Leukaemia and Ph+ Acute Lymphoblastic Leukaemia

Methods

Study Participants

Eligible patients had CML in CP, AP, or BP; or had Ph+ ALL. Patients either:

1) had disease that was resistant to, or were intolerant to, therapy with either dasatinib or nilotinib; or
2) had the BCR-ABL T315I mutation.

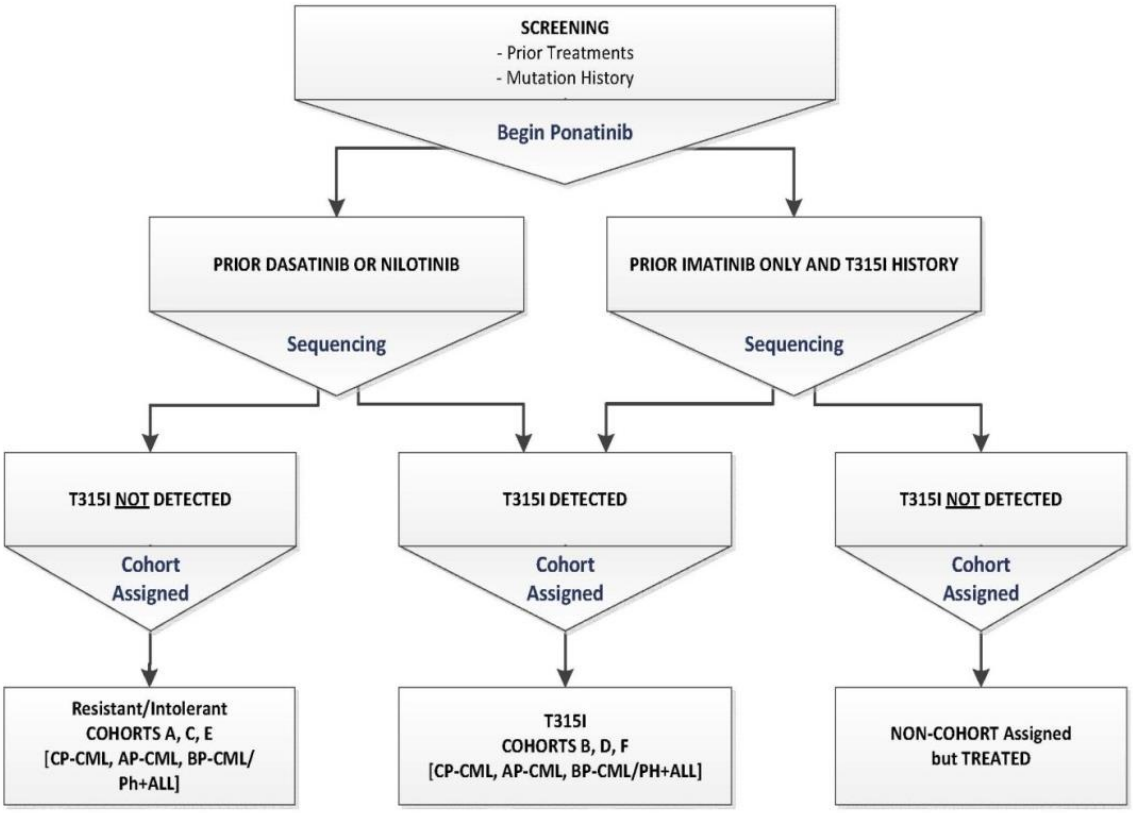
Patients were to remain on treatment for as long as they continue to receive benefit from ponatinib or until disease progression, development of intolerance, patient withdrawal of consent, or decision by the investigator. Patients were grouped in the following cohorts.

Table 12: Ponatinib Phase 2 Study (AP24534-10-201): Patient Cohorts

	CP-CML	AP-CML	BP-CML/Ph+ ALL
Resistant or intolerant to dasatinib or nilotinib	Cohort A	Cohort C	Cohort E
T315I mutation	Cohort B	Cohort D	Cohort F

Source: AP24534-10-201 CSR, Appendix 16.1.1 Protocol
ALL=acute lymphoblastic leukaemia, AP=accelerated phase, BP=blast phase, CML=chronic myeloid leukaemia, CP=chronic phase, Ph+=Philadelphia chromosome-positive

Cohort assignment



The definitions of resistance and intolerance to previous TKI therapy are summarised in the table below.

Table 13: Ponatinib Phase 2 Study: Definitions of Resistance and Intolerance

Definition of	CP-CML	AP-CML	BP-CML/Ph+ ALL
Resistance to dasatinib or nilotinib	Patients had to meet 1 of the following: • Three months after the initiation of therapy: No cytogenetic response (>95% Ph+) or failure to achieve CHR • Six months after the initiation of therapy: Less than a minor cytogenetic response (>65% Ph+) • Twelve months after the initiation of therapy: Less than a PCyR (>35% Ph+) • At any time after the initiation of therapy, the development of new BCR-ABL kinase domain mutations in the absence of CCyR • At any time after the initiation of therapy, the development of new clonal evolution in the absence of CCyR • At any time after the initiation of therapy, the loss of any cytogenetic response [from complete (0%), partial (1% to 35%), minor (36% to 65%), or minimal (66% to 95%) to a response at least 1 grade worse], confirmed in at least 2 consecutive analyses, separated by at least 4 weeks • At any time after the initiation of therapy, progression of disease (to AP or BP)	Patients had to meet 1 of the following: • Three months after the initiation of therapy: failure to achieve a MaHR • At any time after the initiation of therapy, the loss of a MaHR, confirmed in at least 2 consecutive analyses, separated by at least 4 weeks • At any time after the initiation of therapy, the development of new BCR-ABL kinase domain mutations in the absence of a MaHR	Patients had to meet 1 of the following: • One month after the initiation of therapy: failure to achieve a MaHR • At any time after the initiation of therapy, the loss of a MaHR, confirmed in at least 2 consecutive analyses, separated by at least 1 week • At any time after the initiation of therapy, the development of new BCR-ABL kinase domain mutations in the absence of a MaHR
Intolerance	Defined as: Non-hematologic intolerance: Patients with grade 3 or 4 toxicity while on therapy, or with persistent grade 2 toxicity, unresponsive to optimal management, including dose adjustments (unless dose reduction was not considered in the best interest of the patient if response was already suboptimal) in the absence of a CCyR for CP patients or MaHR for AP, BP or Ph+ ALL patients. Hematologic intolerance: Patients with grade 3 or 4 toxicity (ANC or platelets) while on therapy that was recurrent after dose reduction to the lowest doses recommended by manufacturer (80 mg QD for dasatinib; 400 mg QD for nilotinib) in the absence of a CCyR for CP patients or MaHR for AP, BP or Ph+ ALL patients.		

Source AP24534-10-201 CSR Appendix 16.1.1 Protocol and Baccarani et al, 2009
CP=chronic phase, CML=Chronic myeloid leukaemia, AP=accelerated phase, BP=blast phase, Ph+=Philadelphia chromosome positive, ALL=acute lymphoblastic leukaemia, CHR=complete hematologic response, PCyR=partial cytogenetic response, CCyR=complete cytogenetic response, MaHR=major hematologic response, ANC=absolute neutrophil count, QD=once daily.

Key inclusion criteria

1. CML in any phase (CP, AP, or BP of any phenotype) or Ph+ ALL, and either be previously treated with and resistant/intolerant to either dasatinib or nilotinib, or developed the T315I mutation after any TKI therapy.
2. ≥18 years old.
3. ECOG performance status ≤ 2.

4. Adequate renal function defined as serum creatinine < 1.5× upper limit of normal (ULN) for institution.
5. Adequate hepatic function defined as: a. Total bilirubin <1.5 × ULN, b. Alanine aminotransferase and aspartate aminotransferase < 2.5 × ULN for institution (< 5 x ULN if liver involvement with leukemia), c. Prothrombin time < 1.5 × ULN.
6. Normal pancreatic status defined as: a. Lipase ≤ 1.5 × ULN, b. Amylase ≤ 1.5 × ULN.
7. QTcF of ≤ 450 ms in males or ≤ 470 ms in females on screening.

Key exclusion criteria

1. Underwent autologous or allogeneic stem cell transplant < 60 days prior to receiving the first dose of ponatinib; any evidence of on-going graft-versus-host disease (GVHD), or GVHD requiring immunosuppressive therapy.
2. Take medications that are known to be associated with Torsades de Pointes.
3. Patient with CML CP are excluded if they are in CCyR; Patients with CML AP, BP, or Ph+ ALL are excluded if they are in MaHR.
4. Have active central nervous system disease as evidenced by cytology or pathology.
5. Have significant or active cardiovascular disease.
6. Have a history of pancreatitis or alcohol abuse.
7. Have uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL).
8. Are pregnant or lactating.

Treatments

Study drug (ponatinib) was self-administered by the patient at a starting dose of 45 mg taken orally once daily. Patients were requested to take the prescribed number of tablets with or without food at approximately the same time each day. Patients were instructed not to eat or drink anything other than water for 2 hours after taking the tablets. Each 28-day dosing period is termed 1 cycle.

Doses could be held for up to 28 days or reduced per the protocol to manage adverse reactions; lowest dose was 15 mg daily.

Objectives

Primary Objective

- To determine the efficacy of ponatinib in Ph+ leukemia patients who are resistant or intolerant to either dasatinib or nilotinib or have the T315I mutation

Secondary Objectives

- To further characterise anti-leukemic activity of ponatinib by clinical responses, molecular responses, and clinical outcomes
- Molecular genetic status of patients
- Safety

Outcomes/endpoints

Primary endpoints

- For CML patients in CP at study entry: MCyR, defined as CCyR or PCyR.

- For CML patients in AP at study entry: MaHR, defined as CHR or no NEL.
- For CML patients in BP at study entry or Ph+ ALL patients: MaHR, consisting of CHR or NEL.

Secondary endpoints

- For CML patients in CP:
  - Hematologic responses: CHR;
  - Cytogenetic responses: confirmed MCyR; and
  - Molecular responses: MMR.
- For CML patients in AP or BP or Ph+ ALL patients:
  - Cytogenetic responses: CCyR, PCyR, confirmed MCyR; and
  - Molecular responses: MMR.
- For all patients: time to response, duration of response, progression free survival, and overall survival.
- For all patients: safety and tolerability.

Exploratory endpoints

- For all patients: BCR-ABL sequence collection and analysis
- For all patients: ASO PCR for T315I
- For all patients: molecular genetic analyses.

The definitions of the response criteria are summarised in the table below.

Table 14: Ponatinib Phase 1 and Phase 2 Studies: Definitions of Response Criteria

Disease	Type of Response	
CP-CML	**Complete Hematologic Response (CHR)**	
	▪ White blood count (WBC) ≤ institutional upper limit of normal (ULN) ▪ Platelets <450,000/mm³ ▪ No blasts or promyelocytes in peripheral blood ▪ <5% myelocytes plus metamyelocytes in peripheral blood ▪ Basophils <5% in peripheral blood ▪ No extramedullary involvement (including no hepatomegaly or splenomegaly)	
AP-CML, BP-CML and Ph+ ALL	**Major hematologic response (MaHR)**	
	Complete Hematologic Response (CHR)	**No Evidence of Leukaemia (NEL)**
	▪ White blood count (WBC) ≤institutional upper limit of normal (ULN) ▪ Absolute neutrophil count (ANC) ≥1000/mm³ ▪ Platelets ≥100,000/ mm³ ▪ No blasts or promyelocytes in peripheral blood ▪ Bone marrow blasts ≤5% ▪ <5% myelocytes plus metamyelocytes in peripheral blood ▪ Basophils <5% in peripheral blood ▪ No extramedullary involvement (including no hepatomegaly or splenomegaly)	▪ WBC ≤institutional ULN ▪ No blasts or promyelocytes in peripheral blood ▪ Bone marrow blasts ≤5% ▪ <5 % myelocytes plus metamyelocytes in peripheral blood ▪ Basophils <5% in peripheral blood ▪ No extramedullary involvement (including no hepatomegaly or splenomegaly) ▪ At least one of the following: (i) 20,000/mm³ ≤ platelets < 100,000/mm³ (ii) 500/mm³ ≤ ANC < 1000/mm³
CML (all phases) and Ph+ ALL	**Major Cytogenetic Response (MCyR)**	
	Defined as CCyR+PCyR	
	Complete Cytogenetic Response (CCyR)	
	Defined as no Ph+ cells	
	Partial Cytogenetic Response (PCyR)	
	Defined as 1% to 35% Ph+ cells	
CML (all phases) and Ph+ ALL	**Major Molecular Response (MMR)**	
	Defined as a ≤0.1% ratio of BCR-ABL to ABL transcripts on the International Scale (IS) (i.e., ≤0.1% BCR-ABL^{IS}; patients must have the b2a2/b3a2 (p210) transcript), in peripheral blood measured by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR)	
	Molecular Response 4 (MR4)	
	Defined as ≤0.01% BCR-ABL^{IS} in peripheral blood measured by qRT-PCR	
	Complete Molecular Response (CMR4.5)	
	Undetectable BCR-ABL transcripts in peripheral blood with a ≥4.5 log sensitivity on the IS, measured by qRT-PCR	
BP-CML and Ph+ ALL	**Bone Marrow MMR**	
	Defined as a ≤0.1% ratio of BCR-ABL to ABL transcripts on the International Scale (IS) (i.e., ≤0.1% BCR-ABL^{IS}; patients must have the b2a2/b3a2 (p210) transcript), in bone marrow measured by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR)	
Source: (Talpaz et al, 2006) (hematologic and cytogenetic responses in CML); (Kantarjian et al, 2002) (cytogenetic responses in CML and Ph+ ALL); (Hughes et al, 2006) (molecular response in CML and Ph+ ALL).		

Sample size

Cohort A (R/I CP-CML): 100 patients would provide at least 85% power to distinguish between a null response rate of 20% and an alternative response rate of 35%.

Cohort B (T315I CP-CML): 60 patients would provide approximately 98% power to distinguish between a null response rate of 10% and an alternative response rate of 35%.

Cohorts C to F (R/I and T315I AP-CML, and BP-CML/Ph+ ALL): 40 patients in each cohort (160 patients total) would provide approximately 89% power to distinguish between the null response rate of 10% and an alternative response rate of 30%.

An anticipated higher relative proportion of R/I patients to T315I patients required over-enrolment of the R/I cohorts (Cohorts A, C, and E) to ensure full T315I patient enrolment. At the time of the most recent protocol amendment, it was anticipated that the trial would require up to 450 patients to ensure reaching the planned sample sizes of the T315I cohorts.

Ponatinib Phase 2 Study: Patient Cohorts

	CP-CML	**AP-CML**	**BP-CML/Ph+ ALL**
Resistant/intolerant (R/I) to dasatinib or nilotinib	**Cohort A** N=203 (actual) (planned 100)	**Cohort C** N=65 (actual) (planned 40)	**Cohort E** N=48 (actual) (planned 40)
T315I mutation	**Cohort B** N=64 (actual) (planned 60)	**Cohort D** N=18 (actual) (planned 40)	**Cohort F** N=46 (actual) (planned 40)
CP-CML=chronic phase chronic myeloid leukaemia; AP-CML=accelerated phase chronic myeloid leukaemia; BP=blast phase chronic myeloid leukaemia; Ph+ ALL=Philadelphia chromosome positive acute lymphoblastic leukaemia. Note: 5 additional patients were non-cohort assigned as they had failed imatinib and had a history of T315I, but the mutation was not detected at study entry.			

Randomisation and blinding (masking)

This is an open label uncontrolled study. At enrolment patients were assigned to 1 of the 6 cohorts in accordance with disease diagnosis (CP-CML, AP-CML or BP-CML/Ph+ ALL) and, when the mutations test results were available, presence of the T315I mutation (yes or no).

Statistical methods

Regarding efficacy, each cohort of patients was to be analysed separately. No adjustments for multiplicity were applied. The primary endpoints of MCyR rate and MaHR rate respectively were analysed using a 2-sided exact 95% confidence interval based on all treated patients. For primary and secondary analyses data handling rules were pre-defined for each cohort. Patients who did not meet the criteria for MCyR or the criteria for MaHR respectively were analysed as non-responders.

<u>Data handling rules cohort A and B</u>

For analyses of cytogenetic response, patients with <20 metaphases examined at baseline (including missing baseline cytogenetic assessments), or CCyR at baseline were analysed as non-responders in the primary analysis. For analyses of hematologic response (CHR), patients who entered the trial in CHR and continued to meet CHR criteria on study also were analysed as responders. For MMR, patients for whom

a valid baseline MMR assessment was missing or who met the criteria for MMR at baseline were analysed as non-responders.

Data handling rules cohort C through F

For analyses of hematologic response (MaHR), patients for whom baseline bone marrow blasts could not be determined were analysed as non-responders, and patients who entered the trial in MaHR were analysed as non-responders in the primary analysis. For MMR measured in peripheral blood, patients for whom a valid baseline MMR assessment was missing or who met the criteria for MMR at baseline were analysed as non-responders. For BP-CML/Ph+ALL, MMR was also assessed in bone marrow—in this analysis, patients for whom a valid baseline MMR assessment was missing or who met the criteria for MMR at baseline were analysed according to their on-study assessments. For analyses of cytogenetic response, patients with <20 metaphases examined at baseline, CCyR at baseline, or missing baseline cytogenetic assessments were analysed as non-responders.

In addition, patients should have showed response within 6 months (MaHR) or 12 months (MCyR) after initiation of study treatment, otherwise they were to be classified as non-responders.

According to the Statistical Analysis Plan the primary analyses were to be based on the per protocol populations with sensitivity analyses based on the Treated population. The Treated population included all patients assigned to one of the Cohorts A through F who had received at least 1 dose of study drug. The per protocol cytogenetic population included all patients in the treated population with a baseline cytogenetic assessment with at least 20 metaphases examined. Patients with <20 metaphases examined at baseline, CCyR at baseline, or missing baseline cytogenetic assessments were excluded. The per protocol hematologic population included all patients in the treated population in Cohorts C through F with a baseline BM assessment for which the percentage of BM blasts was determinable. Patients with missing baseline bone marrow blasts or MaHR at baseline were excluded.

Several sensitivity analyses were planned, among them one based on the original planned sample size in cohorts with an over-enrolment of patients.

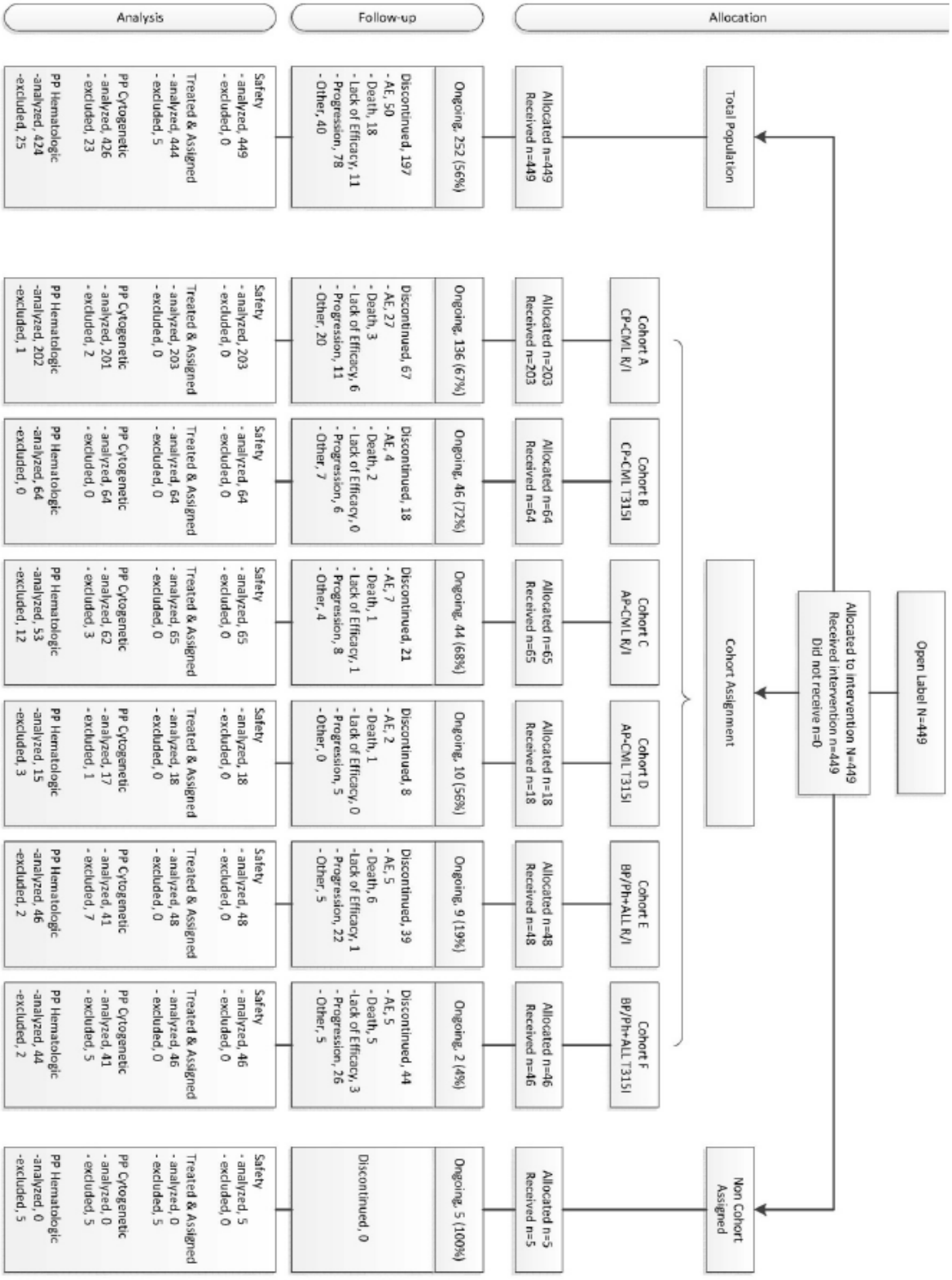
Duration of response, progression-free survival, overall survival and time to response were estimated using the Kaplan-Meier method and, pre-defined censoring rules.

Patients who were not confirmed to have a detectable T315I mutation and who were not resistant or intolerant to dasatinib or nilotinib were analysed separately.

The Safety population included all patients who received at least 1 dose of study drug. In the analyses of safety, data from all cohorts were to be pooled.

Results

Participant flow



Recruitment

A total of 449 patients, whereof 444 eligible, were enrolled from 21 September 2010 to 04 October 2011. Patients were recruited at 68 sites in Australia, Belgium, Canada, France, Germany, Italy, South Korea, United Kingdom, United States, the Netherlands, Spain, and Sweden.

Conduct of the study

Protocol deviations

Major protocol deviations that occurred are summarised in the table below.

Table 15: Major protocol deviations: safety population

Protocol Deviation	Total Safety Population N = 449[a] n (%)	CP-CML[a] N = 270 n (%)	AP-CML[a] N = 85 n (%)	BP-CML/ Ph+ALL N = 94 n (%)
Bone marrow cytogenetics at baseline for CP-CML patient contained <20 evaluable metaphases	N/A	2 (0.7)	N/A	N/A
AP-CML/BP-CML/Ph+ ALL patients with MaHR at baseline	N/A	N/A	14 (16.5)	0
Bone marrow aspiration not performed for AP-CML/BP-CML/Ph+ ALL patients post-baseline[b]	N/A	N/A	0	4 (4.3)
Bone marrow cytogenetics not performed for CP-CML patients post-baseline[c]	N/A	2 (0.7)	N/A	N/A
End of treatment visit missed w/o withdrawal of consent by patient	27 (6.0)	8 (3.0)	6 (7.1)	13 (13.8)
Duration between 2 consecutive bone marrow assessments for AP-CML/BP-CML/Ph+ ALL patients greater than 4 months	N/A	N/A	15 (17.6)	3 (3.2)
Duration between 2 consecutive cytogenetic assessments for CP-CML patients greater than 6 months	N/A	8 (3.0)	N/A	N/A

Source: Section 14: Table 14.1.1.3.2. Database cutoff date: 27 April 2012.
a Includes 5 non-cohort assigned patients (3 CP-CML and 2 AP-CML).
b Excludes patients who discontinued within 30 days after the first dose of ponatinib.
c Excludes patients who discontinued within 90 days after the first dose of ponatinib.
ALL=acute lymphoblastic leukemia, AP=accelerated phase, BP=blast phase, CML=chronic myeloid leukemia, CP=chronic phase, Ph+=Philadelphia chromosome positive, R/I=resistant or intolerant.

Protocol amendments

The original protocol was approved on 16 July 2010 (study initiation 21 September 2010)

- Protocol Amendment 1 was dated 27 October 2010

Response criteria were updated.

- Protocol Amendment 2 was dated 08 April 2011

As early enrolment experience demonstrated over-availability of R/I patients compared with T315I patients, the amendment served to increase the overall sample size of the study to allow for over-enrolment in the R/I cohorts to ensure full patient enrolment in the T315I cohorts.

- Protocol Amendment 3 was dated 24 May 2012

No important change.

Baseline data

Table 16: Demographics and Baseline Characteristics

Patient Characteristics	CP-CML		AP-CML		BP-CML/Ph+ ALL		Non-Cohort Assigned N=5[a]
	R/I N=203	T315I N=64	R/I N=65	T315I N=18	R/I N=48	T315I N=46	
Age							
Median, years (min – max)	61.0 (22 - 94)	51.0 (18 - 87)	60.0 (23 - 82)	54.0 (24 - 78)	54.0 (18 - 74)	56.0 (18 - 80)	63.0 (51 - 71)
18 - 44 years (%)	31 (15.3)	24 (37.5)	16 (24.6)	5 (27.8)	16 (33.3)	17 (37.0)	0
45 - 64 years (%)	90 (44.3)	22 (34.4)	28 (43.1)	8 (44.4)	18 (37.5)	16 (34.8)	3 (60.0)
≥ 65 years (%)	82 (40.4)	18 (28.1)	21 (32.3)	5 (27.8)	14 (29.2)	13 (28.3)	2 (40.0)
Gender							
Male, n (%)	95 (46.8)	48 (75.0)	25 (38.5)	11 (61.1)	31 (64.6)	26 (56.5)	2 (40.0)
Geographical Region							
North America (US and Canada)	85 (41.9)	26 (40.6)	30 (46.2)	6 (33.3)	35 (72.9)	24 (52.2)	0
Europe/Australia	104 (51.2)	26 (40.6)	30 (46.2)	10 (55.6)	6 (12.5)	20 (43.5)	3 (60.0)
Asia	14 (6.9)	12 (18.8)	5 (7.7)	2 (11.1)	7 (14.6)	2 (4.3)	2 (40.0)
Race, n (%)							
American Indian/Alaska native	1 (0.5)	0	1 (1.5)	0	0	0	0
Asian	17 (8.4)	14 (21.9)	8 (12.3)	3 (16.7)	8 (16.7)	7 (15.2)	2 (40.0)
Black/African American	7 (3.4)	4 (6.3)	7 (10.8)	5 (27.8)	1 (2.1)	1 (2.2)	0
Native Hawaiian/Pacific Islander	0	0	0	0	0	0	0
White	174 (85.7)	42 (65.6)	47 (72.3)	9 (50.0)	39 (81.3)	38 (82.6)	3 (60.0)
Unknown	3 (1.5)	3 (4.7)	2 (3.1)	0	0	0	0
Other	1 (0.5)	1 (1.6)	0	1 (5.6)	0	0	0
Ethnicity							
Hispanic/Latino	13 (6.4)	8 (12.5)	6 (9.2)	1 (5.6)	2 (4.2)	12 (26.1)	0
Not Hispanic/Latino	190 (93.6)	56 (87.5)	59 (90.8)	17 (94.4)	46 (95.8)	34 (73.9)	5 (100.0)
ECOG Performance Status[b]							
ECOG=0, n (%)	139 (68.5)	47 (73.4)	33 (50.8)	12 (66.7)	15 (31.3)	16 (34.8)	5 (100.0)
ECOG=1, n (%)	60 (29.6)	17 (26.6)	25 (38.5)	6 (33.3)	20 (41.7)	19 (41.3)	0
ECOG=2, n (%)	4 (1.9)	0	7 (10.8)	0	12 (25.0)	11 (23.9)	0
Time Since Diagnosis							
Median time, years (min - max)	7.77 (0.45 - 27.43)	4.78 (1.16 - 19.49)	7.13 (0.33 - 28.47)	6.61 (1.17 - 15.90)	3.96 (0.62 - 27.21)	1.63 (0.46 - 14.14)	4.80 (1.74 - 18.60)
0 to <5 years (%)	71 (35.0)	33 (51.6)	23 (35.4)	5 (27.8)	27 (56.3)	35 (76.1)	3 (60.0)
5 to <10 years (%)	49 (24.1)	22 (34.4)	16 (24.6)	8 (44.4)	11 (22.9)	7 (15.2)	1 (20.0)
≥ 10 years (%)	83 (40.9)	9 (14.1)	26 (40.0)	5 (27.8)	10 (20.8)	4 (8.7)	1 (20.0)

a Includes 3 CP-CML and 2 AP-CML patients.
b 1 missing from BP-CML/Ph+ALL R/I cohort.

Table 17: Prior Cancer (Non TKI) Treatments (>2%)

Prior Cancer Treatment >2% Incidence Total Safety Population	CP-CML		AP-CML		BP-CML/Ph+ ALL		Non-Cohort Assigned N=5[a]
	R/I N=203	T315I N=64	R/I N=65	T315I N=18	R/I N=48	T315I N=46	
Chemotherapy							
Hydroxycarbamide	110 (54.2)	35 (54.7)	35 (53.8)	13 (72.2)	20 (41.7)	17 (37.0)	3 (60.0)
Cytarabine	41 (20.2)	4 (6.3)	13 (20.0)	7 (38.9)	15 (31.3)	21 (45.7)	1 (20.0)
Omacetaxine (HHT)	18 (8.9)	5 (7.8)	12 (18.5)	2 (11.1)	3 (6.3)	0	1 (20.0)

Prior Cancer Treatment >2% Incidence Total Safety Population	CP-CML		AP-CML		BP-CML/Ph+ ALL		Non-Cohort Assigned N=5[a]
	R/I N=203	T315I N=64	R/I N=65	T315I N=18	R/I N=48	T315I N=46	
Vincristine	0	0	0	0	7 (14.6)	21 (45.7)	0
Cyclophosphamide	1 (0.5)	0	0	0	8 (16.7)	12 (26.1)	0
Methotrexate	0	0	1 (1.5)	0	5 (10.4)	15 (32.6)	0
Daunorubicin	2 (1.0)	0	1 (1.5)	0	6 (12.5)	6 (13.0)	0
Mercaptopurine	3 (1.5)	0	2 (3.1)	0	3 (6.3)	7 (15.2)	0
Idarubicin	1 (0.5)	0	4 (6.2)	1 (5.6)	3 (6.3)	5 (10.9)	0
Doxorubicin	0	0	0	0	3 (6.3)	9 (19.6)	0
Asparaginase	0	0	0	0	3 (6.3)	6 (13.0)	0
Busulfan	5 (2.5)	0	2 (3.1)	0	1 (2.1)	1 (2.2)	0
Etoposide	1 (0.5)	0	2 (3.1)	0	3 (6.3)	3 (6.5)	0
Other Cancer Agents							
Interferon	89 (43.8)	13 (20.3)	28 (43.1)	7 (38.9)	8 (16.7)	3 (6.5)	3 (60.0)
Prednisone	0	0	0	0	3 (6.3)	10 (21.7)	0
Dexamethasone	0	0	0	0	2 (4.2)	10 (21.7)	0
Cytarabine and Interferon							
Cytarabine and interferon	36 (17.7)	2 (3.1)	10 (15.4)	6 (33.3)	4 (8.3)	0	0
Cytarabine only	5 (2.5)	2 (3.1)	3 (4.6)	1 (5.6)	11 (22.9)	21 (45.7)	0
Interferon only	53 (26.1)	11 (17.2)	18 (27.7)	1 (5.6)	4 (8.3)	3 (6.5)	1 (20.0)
Other Therapies							
Stem Cell Transplant	11 (5.4)	1 (1.6)	6 (9.2)	2 (11.1)	11 (22.9)	9 (19.6)	0

a Includes 3 CP-CML and 2 AP-CML patients.
HHT=Homoharringtonine.

Table 18: Prior TKIs

Prior TKIs	CP-CML		AP-CML		BP-CML/ Ph+ ALL		Non-Cohort Assigned N=5[a]
	R/I N=203	T315I N=64	R/I N=65	T315I N=18	R/I N=48	T315I N=46	
Number of prior TKIs							
Median number, n (min - max)	3.0 (1 - 5)	2.0 (1 - 4)	3.0 (1 - 5)	2.5 (1 - 4)	3.0 (1 - 4)	2.0 (1 - 3)	1.0 (1 - 2)
None	0	0	0	0	0	0	0
1	4 (2.0)	11 (17.2)	1 (1.5)	3 (16.7)	2 (4.2)	7 (15.2)	4 (8.0)
2	64 (31.5)	27 (42.2)	22 (33.8)	6 (33.3)	13 (27.1)	22 (47.8)	1 (20.0)
≥ 3	135 (66.5)	26 (40.6)	42 (64.6)	9 (50.0)	33 (68.8)	17 (37.0)	0
Prior Approved TKIs							
Imatinib	196 (96.6)	62 (96.9)	64 (98.5)	18 (100.0)	46 (95.8)	39 (84.8)	5 (100.0)
Imatinib only	0	10 (15.6)	0	3 (16.7)	0	3 (6.5)	5 (100.0)
Dasatinib	176 (86.7)	41 (64.1)	55 (84.6)	15 (83.3)	45 (93.8)	43 (93.5)	0 (0)
Dasatinib only	4 (2.0)	1 (1.6)	0	0	2 (4.2)	4 (8.7)	0
Nilotinib	151 (74.4)	33 (51.6)	47 (72.3)	9 (50.0)	36 (75.0)	18 (39.1)	0
Nilotinib only	1 (0.5)	0	1 (1.5)	0	0	0	0
Imatinib only OR Dasatinib only OR Nilotinib only	5 (2.5)	11 (17.2)	1 (1.5)	3 (16.7)	2 (4.2)	7 (15.2)	5 (100.0)
Imatinib + (Nilotinib OR Dasatinib)	74 (27.7)	31 (11.6)	27(10.1)	6 (33.3)	13 (4.9)	21 (45.7)	0
Dasatinib + Nilotinib (w/o Imatinib)	2 (1.0)	0	0	0	0	3 (6.5)	0
Imatinib + Dasatinib + Nilotinib	122 (60.1)	21 (32.8)	37 (56.9)	9 (50.0)	33 (68.8)	15 (32.6)	0
Prior Investigational TKIs							
Bosutinib	22 (10.8)	2 (3.1)	4 (6.2)	0	3 (6.3)	1 (2.2)	1 (20.0)

Bafetinib (INNO-406)	5 (2.5)	0	2 (3.1)	1 (5.6)	0	0	0
Tozasertib	0	2 (3.1)	0	0	0	0	0
Danusertib	0	0	0	0	0	1 (2.2)	0
XL228	4 (2.0)	1 (1.6)	2 (3.1)	0	0	0	0
DCC-2036	2 (1.0)	2 (3.1)	3 (4.6)	1 (5.6)	0	0	0
Radotinib	5 (2.5)	2 (3.1)	2 (3.1)	0	0	0	0
a Includes 3 CP-CML and 2 AP-CML patients.							

Numbers analysed

Predefined analysis populations included: 1) the safety population, 2) the treated population 3) the per protocol cytogenetic population, and 4) the per protocol hematologic population.

The "safety population" (N=449) included all patients who received at least 1 dose of study drug.

The "treated population" (N=444) included all patients assigned to Cohorts A through F who received at least 1 dose of study drug. There were 267 CP-CML patients (R/I Cohort A: n=203, T315I Cohort B: n=64), 83 AP-CML patients (R/I Cohort C: n=65, T315I Cohort D: n=18), and 94 BP-CML/Ph+ ALL patients (R/I Cohort E: n=48, T315I Cohort F: n=46) in the treated population.

The "per protocol cytogenetic population" included all patients in the treated population with a baseline cytogenetic assessment with at least 20 metaphases examined and who did not enter in CCyR. Patients whose baseline cytogenetic status was missing were excluded from the analysis. There were 265 CP-CML patients (R/I Cohort A: n=201, T315I Cohort B: n=64), 79 AP-CML patients (R/I Cohort C: n=62, T315I Cohort D: n=17), and 82 BP-CML/Ph+ ALL patients (R/I Cohort E: n=41, T315I Cohort F: n=41) in the per protocol cytogenetic population.

The per protocol hematologic population included all patients in the treated population in Cohorts C through F with a baseline BM assessment for which the percentage of BM blasts was determinable and who did not have MaHR at baseline. There were 68 AP-CML patients (R/I Cohort C: n=53, T315I Cohort D: n=15), and 90 BP-CML/Ph+ ALL patients (R/I Cohort E: n=46, T315I Cohort F: n=44) in the per protocol hematologic population.

Outcomes and estimation

The pivotal study being a non-randomised study has the limitation of not having a comparator arm. However an internal comparison is possible by looking at the study population previous response to the most recent other TKIs. This is summarised in the table below.

Table 19: Best response to most recent dasatinib or nilotinib: Treated population

Endpoint	Total N=427[a]	CP-CML R/I N=203	CP-CML T315I N=53[a]	AP-CML R/I N=65	AP-CML T315I N=15[a]	BP-CML/Ph+ ALL R/I N=48	BP-CML/Ph+ ALL T315I N=43[a]	Non-Cohort Assigned N=0[a, b]
Molecular Response								
CMR	4 (0.9)	1 (0.5)	1 (1.9)	0	0	1 (2.1)	1 (2.3)	0
MMR	12 (2.8)	6 (3.0)	0	1 (1.5)	1 (6.7)	1 (2.1)	3 (7.0)	0
Cytogenetic Response								
MCyR[c]	77 (18.0)	46 (22.7)	12 (22.6)	8 (12.3)	2 (13.3)	5 (10.4)	4 (9.3)	0
CCyR	46 (10.8)	23 (11.3)	10 (18.9)	6 (9.2)	1 (6.7)	4 (8.3)	2 (4.7)	0
PCyR	31 (7.3)	23 (11.3)	2 (3.8)	2 (3.1)	1 (6.7)	1 (2.1)	2 (4.7)	0
Less than PCyR	49 (11.5)	28 (13.8)	9 (17.0)	9 (13.8)	2 (13.3)	1 (2.1)	0	0
Hematologic Response								
MaHR (AP, BP, Ph+ALL)	13 (3.0)	1 (0.5)	0	5 (7.7)	0	5 (10.4)	2 (4.7)	0
CHR (CP)	81 (19.0)	56 (27.6)	8 (15.1)	16 (24.6)	0	0	1 (2.3)	0

Source: Section 14 Table 14.1.4. Database cutoff date 27 April 2012.
a Denominator includes only patients in the cohort who received prior dasatinib or nilotinib therapy
b This group comprises 5 non-cohort assigned patient (3 CP-CML and 2 AP-CML), none of whom received prior dasatinib or nilotinib.
c MCyR=CCyR+PCyR.
ALL=acute lymphoblastic leukemia, AP=accelerated phase, BP=blast phase, CHR=complete hematologic response, CML=chronic myeloid leukemia, CMR=complete molecular response, CP=chronic phase, MaHR=major hematologic response, MCyR=major cytogenetic response, MMR=major molecular response, PCyR=partial cytogenetic response, Ph+=Philadelphia chromosome-positive.

Table 20: Efficacy of Iclusig in resistant or intolerant chronic phase CML patients

	Overall (N=267)	Resistant or Intolerant	
		R/I Cohort (N=203)	T315I Cohort (N=64)
Cytogenetic Response			
Major (MCyR) [a] % (95% CI)	54% (48-60)	49% (42-56)	70% (58-81)
Complete (CCyR) % (95% CI)	44% (38-50)	37% (31-44)	66% (53-77)
Major Molecular Response [b] % (95% CI)	30% (24-36)	23% (18-30)	50% (37-63)

[a] Primary endpoint for CP-CML Cohorts was MCyR, which combines both complete (No detectable Ph+ cells) and partial (1% to 35% Ph+ cells) cytogenetic responses.
[b] Measured in peripheral blood. Defined as a ≤0.1% ratio of BCR-ABL to ABL transcripts on the International Scale (IS) (ie, ≤0.1% BCR-ABL^{IS}; patients must have the b2a2/b3a2 (p210) transcript), in peripheral blood measured by quantitative reverse transcriptase polymerase chain reaction (qRT PCR).

Table 21: Efficacy of Iclusig in resistant or intolerant advanced phase CML patients

	Accelerated Phase CML			Blast Phase CML		
	Overall (N=83)	Resistant or Intolerant		Overall (N=62)	Resistant or Intolerant	
		R/I Cohort (N=65)	T315I Cohort (N=18)		R/I Cohort (N=38)	T315I Cohort (N=24)
Haematological Response Rate						
Major[a] (MaHR) % (95% CI)	58% (47-69)	60% (47-72)	50% (26 - 74)	31% (20 – 44)	32% (18 – 49)	29% (13 – 51)
Complete[b] (CHR) % (95% CI)	47% (36-58)	46% (34-49)	50% (26-74)	21% (12-33)	24% (11-40)	17% (5-37)
Major Cytogenetic Response[c] % (95% CI)	39% (28-50)	34% (23-47)	56% (31-79)	23% (13-35)	18% (8-34)	29% (13-51)

[a] Primary endpoint for AP-CML and BP-CML/Ph+ ALL Cohorts was MaHR, which combines complete haematological responses and no evidence of leukaemia.
[b] CHR: WBC ≤ institutional ULN, ANC ≥1000/mm^3, platelets ≥100,000/mm^3, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils <5% in peripheral blood, No extramedullary involvement (including no hepatomegaly or splenomegaly).
[c] MCyR combines both complete (No detectable Ph+ cells) and partial (1% to 35% Ph+ cells) cytogenetic responses.

Table 22: Efficacy of Iclusig in resistant or intolerant Ph+ ALL patients

	Overall (N=32)	Resistant or Intolerant	
		R/I Cohort (N=10)	T315I Cohort (N=22)
Haematological Response Rate			
Major[a] (MaHR) % (95% CI)	41% (24-59)	50% (19-81)	36% (17-59)
Complete[b] (CHR) % (95% CI)	34% (19-53)	40% (12-73)	32% (14-55)
Major Cytogenetic Response[c] % (95% CI)	47% (29-65)	60% (26-88)	41% (21-64)

[a] Primary endpoint for AP-CML and BP-CML/Ph+ ALL Cohorts was MaHR, which combines complete haematological responses and no evidence of leukaemia.
[b] CHR: WBC ≤ institutional ULN, ANC ≥1000/mm^3, platelets ≥100,000/mm^3, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils <5% in peripheral blood, No extramedullary involvement (including no hepatomegaly or splenomegaly).
[c] MCyR combines both complete (No detectable Ph+ cells) and partial (1% to 35% Ph+ cells) cytogenetic responses.

Table 23: Response by Prior TKI Therapy: Safety Population (Including Non-Cohort Assigned patients)

	Response Rate, n/N (%)								
	CP-CML			AP-CML			BP-CML/Ph+ALL		
	Total[a]	R/I	T315I	Total[a]	R/I	T315I	Total	R/I	T315I
	Response by 1 Prior Approved TKI								
Hematologic									
CHR	19/19 (100)	5/5 (100)	11/11 (100)	NA	NA	NA	NA	NA	NA
MaHR	NA	NA	NA	5/6 (83.3)	1/1 (100)	2/3 (66.7)	3/9 (33.3)	1/2 (50.0)	2/7 (28.6)
Cytogenetic									
MCyR	16/19 (84.2)	3/5 (60.0)	10/11 (90.0)	6/6 (100)	1/1 (100)	3/3 (100)	5/9 (55.6)	1/2 (50.0)	4/7 (57.1)
CCyR	14/19 (73.7)	2/5 (40.0)	9/11 (81.8)	4/6 (66.7)	1/1 (100)	2/3 (66.7)	3/9 (33.3)	1/2 (50.0)	2/7 (28.6)
Molecular									
MMR	9/19 (47.4)	1/5 (20.0)	7/11 (63.6)	2/6 (33.3)	0/1 (0)	1/3 (33.3)	1/9 (11.1)	1/2 (50.0)	0/7 (0)
	Response by 2 Prior Approved TKIs								
Hematologic									
CHR	104/107 (97.2)	74/76 (97.4)	30/31 (96.8)	NA	NA	NA	NA	NA	NA
MaHR	NA	NA	NA	20/33 (60.6)	18/27 (66.7)	2/6 (33.3)	15/37 (40.5)	7/13 (53.8)	8/24 (33.3)
Cytogenetic									
MCyR	65/107 (60.7)	41/76 (53.9)	24/31 (77.4)	13/33 (39.4)	9/27 (33.3)	4/6 (66.7)	15/37 (40.5)	6/13 (46.2)	9/24 (37.5)
CCyR	55/107 (51.4)	32/76 (42.1)	23/31 (74.2)	8/33 (24.2)	5/27 (18.5)	3/6 (50.0)	11/37 (29.7)	4/13 (30.8)	7/24 (29.2)
Molecular									
MMR	34/107 (31.8)	19/76 (25.0)	15/31 (48.4)	3/33 (9.1)	2/27 (7.4)	1/6 (16.7)	6/37 (16.2)	4/13 (30.8)	2/24 (8.3)
	Response by 3 Prior Approved TKIs								
Hematologic									
CHR	128/143 (89.5)	112/122 (91.8)	16/21 (76.2)	NA	NA	NA	NA	NA	NA
MaHR	NA	NA	NA	25/46 (54.3)	20/37 (54.1)	5/9 (55.6)	14/48 (29.2)	9/33 (27.3)	5/15 (33.3)
Cytogenetic									
MCyR	66/143 (46.2)	55/122 (45.1)	11/21 (52.4)	15/46 (32.6)	12/37 (32.4)	3/9 (33.3)	9/48 (18.8)	6/33 (18.2)	3/15 (20.0)
CCyR	52/143 (36.4)	42/122 (34.4)	10/21 (47.6)	8/46 (17.4)	7/37 (18.9)	1/9 (11.1)	9/48 (18.8)	6/33 (18.2)	3/15 (20.0)
Molecular									
MMR	37/143 (25.9)	27/122 (22.1)	10/21 (47.6)	5/46 (10.9)	4/37 (10.8)	1/9 (11.1)	4/48 (8.3)	4/33 (12.1)	0/15 (0)

Source: Section 14 Table 14.2.4.3.2.1, Table 14.2.4.3.5.1, Table 14.2.4.3.4 and Listing 16.6.1.1, Listing 16.2.1. Database cutoff date 27 April 2012

a Includes 5 non-cohort assigned: 3 CP-CML and 2 AP-CML.

CCyR=complete cytogenetic response, CHR=complete hematologic response, CML=chronic myeloid leukemia, CP=chronic phase, MCyR=major cytogenetic response, R/I=resistant or intolerant, TKI=tyrosine kinase inhibitor. BP=blast phase, R/I=resistant or intolerant, Ph+=Philadelphia chromosome-positive, ALL=acute lymphoblastic leukemia.

For all 6 cohorts in the pivotal study, the pre-specified primary statistical criteria were met, as the 95% CIs of the primary endpoint response rates exceeded and exclude the pre-specified null (uninteresting) values set forth in the protocol.

Ancillary analyses

Time to response was estimated using the Kaplan-Meier method for all patients and for responders only

CP-CML: For the combined CP-CML group, the median time to MCyR (responders only) was 84 days (range 49 to 334 days), and the median time to MMR (responders only) was 167 days (range 55 to 421 days).

AP-CML: For the combined AP-CML group, the median time to MaHR (responders only) was 21 days (range 12 to 176 days), the median time to MCyR (responders only) was 111.5 days (range 25 to 295 days), and the median time to MMR (responders only) was 113 days (range 55 to 343 days).

BP-CML/Ph+ ALL: For the combined AP-CML group, the median time to MaHR (responders only) was 26.0 days (range 11 to 168 days), the median time to MCyR (responders only) was 55 days (range 27 to 168 days), and the median time to MMR (responders only) was 56 days (range 54 to 113 days).

Duration of response was estimated by the Kaplan-Meier method as the probability of remaining in response measured in weeks. This is based on overall median durations of follow-up for Ph+ patients of 14.7 (range 0.1 to 24.9) months with the phase 2 study; and 24.9 (range 0.48 to 44.1) months with the phase 1study. The results are summarised in the tables below.

Table 24: Duration of Cytogenetic and Molecular response CP-CML: AP24534-10-201 (Treated population) and AP24534-07-101

	CP-CML, AP24534-10-201 (Phase 2)			CP-CML, AP24534-07-101 (Phase 1)
	Overall N=267	R/I N=203	T315I N=64	Overall N=45
Cytogenetic Response				
Duration of MCyR				
N	149	104	45	31
Patients who lost MCyR, n (%)	11 (7.4)	11 (10.6)	0 (0)	6 (19.4)
Patients maintaining MCyR, n (%)	138 (92.6)	93 (89.4)	45 (100)	25 (80.6)
Median, days (95% CI)	NR	NR	NR	NR
Range, days (min – max)	1 – 591	1 - 591	1 – 590	56.7 – 1246.7
Probability of remaining in response after 12 months, % (95% CI)	91.4 (85.0, 95.2)	87.6 (78.6, 92.9)	100 (100, 100)	86.9 (68.7, 94.9)
Molecular Response				
Duration of MMR				
N	91	55	36	22
Patients who lost MMR, n (%)	15 (16.5)	11 (20)	4 (11.1)	7 (31.8)
Patients maintaining MMR, n (%)	76 (83.5)	44 (80)	32 (88.9)	15 (68.2)
Median, days (95% CI)	NR	NR	NR	NR
Range, days (min – max)	1 - 590	1 – 589	1 – 590	0.7 – 1155.7
Probability of remaining in response after 12 months, % (95% CI)	80.6 (69.8, 87.9)	76.8 (61.9, 86.5)	87.5 (70.0, 95.1)	73.7 (47.9, 88.1)
Duration of Follow-Up				
Median, days (min – max)	466 (4, 758)	477 (4, 758)	450 (45, 673)	923 (51, 1344)

Source: AP24534-10-201 Table 14.2.5.1.1, Table 14.2.5.1.3, Table 14.1.1.1, Table 14.1.1.1.1. AP24534-07-101 Table 14.2.1.1, Table 14.2.6.1, Figure 14.3.2. Data extraction date 09 November 2012.

Note: The median of the duration of response and 95% confidence intervals are calculated using the Kaplan-Meier method. Patients who did not demonstrate progression or loss of response were censored at the last response assessment date.

CML=chronic myeloid leukemia, CP=chronic phase, MCyR=major cytogenetic response, MMR= major molecular response, R/I=resistant or intolerant, NR=not reached, CI=confidence interval, min=minimum, max=maximum.

Table 25: Duration of Hematologic and Cytogenetic response in AP-CML and BP-CML/Ph+ ALL, AP24534-10-201 (Treated population)

	AP-CML			BP-CML/Ph+ ALL		
	Overall N=83	R/I N=65	T315I N=18	Overall N=94	R/I N=48	T315I N=46
Hematologic Response						
Duration of MaHR						
N	46	37	9	32	17	15
Patients who lost MaHR, n (%)	23 (50.0)	19 (51.4)	4 (44.4)	23 (71.9)	11 (64.7)	12 (80.0)
Patients maintaining MaHR, n (%)	23 (50.0)	19 (48.6)	5 (55.6)	9 (28.1)	6 (35.3)	3 (20.0)
Median, days (95% CI)	360 (211, -)	360 (211, -)	N/R	126 (84, 196)	196 (81, -)	105 (67, 131)
Range, days (min – max)	35 – 654	35 - 654	42 – 598	30 – 597	54 – 597	30 – 418
Probability of remaining in response after 12 months, %	48.4 (32.4, 62.7)	46.6 (28.9, 62.5)	55.6 (20.4, 80.5)	26.4 (12.3, 43.0)	40.3 (17.6, 62.2)	7.8 (0.5, 29.5)
Cytogenetic Response						
Duration of MCyR						
N	32	22	10	29	13	16
Patients who lost MCyR, n (%)	8 (25)	5 (22.7)	3 (30)	11 (37.9	2 (15.4)	9 (56.3)
Patients maintaining MCyR, n (%)	24 (75)	17 (77.3)	7 (70)	18 (62.1)	11 (84.6)	7 (43.8)
Median, days (95% CI)	N/R	N/R	N/R	194 (63 – N/A)	N/R	63 (28, 137)
Range, days (min – max)	1 – 505	1 – 421	28 – 505	1 – 590	1 – 590	1 – 393
Probability of remaining in response after 12 months, %	73.3 (53.5, 85.7)	75.6 (50.8, 89.1)	68.6 (30.5, 88.7)	47.1 (24.3, 67.0)	77.8 (36.5, 93.9)	16.2 (1.2, 47.6)
Duration of Follow-Up						
Median, days (min – max)	482 (110, 758)	482 (110, 758)	432 (129, 757)	188 (2, 647)	200 (2, 647)	183 (3, 550)

Source: AP24534-10-201 Table 14.2.5.1.1, Table 14.2.5.1.2, Table 14.1.1.1, Table 14.1.1.1.1. Data extraction date 09 November 2012.

Note: The median of the duration of response and 95% confidence intervals are calculated using the Kaplan-Meier method. Patients who did not demonstrate progression or loss of response were censored at the last response assessment date.

CML=chronic myeloid leukemia, AP=accelerated phase, BP=blast phase, Ph+=Philadelphia chromosome-positive, ALL=acute lymphoid leukemia, MaHR=major hematologic response, MCyR=major cytogenetic response, R/I=resistant or intolerant, N/A=not available, N/R=not reached, CI=confidence interval, min=minimum, max=maximum.

Table 26: Duration of Hematologic and Cytogenetic response in AP-CML and BP-CML/Ph+ ALL, AP24534-07-101

	AP-CML, BP-CML, Ph+ ALL
	Overall N=22
Hematologic Response	
Duration of MaHR	
N	8
Patients who lost MaHR, n (%)	4 (50)
Patients maintaining MaHR, n (%)	4 (50)
Median, days (95% CI)	109.9 (25.2, 448)
Range, days (min – max)	0.7 – 448
Probability of remaining in response after 12 months, % (95% CI)	44.4 (6.6, 78.5)
Cytogenetic Response	
Duration of MCyR	
N	7
Patients who lost MCyR, n (%)	1 (14.3)
Patients maintaining MCyR, n (%)	6 (85.7)
Median, days (95% CI)	NR (17, -)
Range, days (min – max)	0.7 – 672.7
Probability of remaining in response after 12 months, % (95% CI)	50 (0.6, 91.0)
Duration of Follow-Up	
Median, days (min – max)	82 (15, 1344)

Source: AP24534-07-101 Table 14.2.1.4, Table 14.2.1.3, Figure 14.3.2. Data extraction date: 09 November, 2012.
Note: The median of the duration of response and 95% confidence intervals were calculated using the Kaplan-Meier method. Patients who did not demonstrate progression or loss of response were censored at the last response assessment date.
CML=chronic myeloid leukemia, AP=accelerated phase, BP=blast phase, Ph+=Philadelphia chromosome-positive, ALL=acute lymphoid leukemia, MCyR=major cytogenetic response, R/I=resistant or intolerant, N/A=not available, N/R=not reached, CI=confidence interval, min=minimum, max=maximum.

Duration of MCyR and MMR in CP patients, and MaHR and MCyR in more advanced patients, per number of previous TKIs for each cohort in the 201 study:

The TKIs in this analysis are the 3 TKIs that had received marketing authorization at the time the patients enrolled in the trial: imatinib, dasatinib, and nilotinib. Overall, 29 patients in the treated population had 1 prior TKI, 177 had 2 prior TKIs, and 237 had all 3 TKIs.

Table 27: Duration of MCyR by Number of Prior Approved TKis: CP-CML patients in AP24534-10- 201: Treated population

	CP-CML		
	1 TKI (N=16)	2 TKIs (N=107)	3 TKIs (N=143)
CP-CML, R/I			
N	3	45	56
Patients who lost MCyR, n (%)	0 (0)	3 (6.7)	8 (14.3)
Patients maintaining MCyR, n (%)	3 (100)	42 (93.3)	48 (85.7)
Median, days (95% CI)	NR	NR	NR
Range, days (min – max)	1 – 337	1 – 591	1 – 505
Probability of remaining in response after 12 months, % (95% CI)	NR	92.3 (78.0, 97.5)	83.6 (69.8, 91.5)
CP-CML, T315I			
N	10	24	11
Patients who lost MCyR, n (%)	0 (0)	0 (0)	0 (0)
Patients maintaining MCyR, n (%)	10 (100)	24 (100)	11 (100)
Median, days (95% CI)	NR	NR	NR
Range, days (min – max)	246 – 421	1 – 590	1 – 512
Probability of remaining in response after 12 months, %	100	100	100

Source: AP24534-10-201 Table 14.2.6.12.1.2. Data extraction date 09 November 2012.
Note: The median of the duration of response and 95% confidence intervals are calculated using the Kaplan-Meier method. Patients who did not demonstrate progression or loss of response were censored at the last response assessment date.

Table 28: Duration of MMR by Number of Prior Approved TKIs: CP-CML patients in AP24534-10- 201: Treated population

	CP-CML		
	1 TKI (N=16)	2 TKIs (N=107)	3 TKIs (N=143)
CP-CML, R/I			
N	1	20	34
Patients who lost MMR, n (%)	0 (0)	5 (25)	6 (17.6)
Patients maintaining MMR, n (%)	1 (100)	15 (75)	28 (82.4)
Median, days (95% CI)	NR	NR	NR
Range, days (min – max)	338 – 338	78 – 589	1 – 421
Probability of remaining in response after 12 months, % (95% CI)	NR	74 (48.2, 88.3)	78.3 (57.9, 89.7)
CP-CML, T315I			
N	8	17	11
Patients who lost MMR, n (%)	1 (12.5)	1 (5.9)	2 (18.2)
Patients maintaining MMR, n (%)	7 (87.5)	16 (94.1)	9 (81.8)
Median, days (95% CI)	NR	NR	NR
Range, days (min – max)	1 – 440	1 – 590	1 – 503
Probability of remaining in response after 12 months, % (95% CI)	85.7 (33.4, 97.9)	98.3 (61.3, 99.0)	80 (40.9, 94.6)

Source: AP24534-10-201 Table 14.2.6.12.3.2. Data extraction date 09 November 2012.
Note: The median of the duration of response and 95% confidence intervals are calculated using the Kaplan-Meier method. Patients who did not demonstrate progression or loss of response were censored at the last response assessment date.
CML=chronic myeloid leukemia, CP=chronic phase, MCyR=major cytogenetic response, R/I=resistant or intolerant, N/A=not available, NR=not reached, CI=confidence interval, min=minimum, max=maximum.

Table 29: Duration of MaHR by Number of Prior Approved TKIs: AP-CML patients in AP24534-10- 201: Treated population

	AP CML		
	1 TKI (N=4)	2 TKIs (N=33)	3 TKIs (N=46)
AP-CML, R/I			
N	1	18	18
Patients who lost MaHR, n (%)	0 (0)	11 (61.1)	8 (44.4)
Patients maintaining MaHR, n (%)	1 (100)	7 (38.9)	10 (55.6)
Median, days (95% CI)	NR	289 (124 – N/A)	NR
Range, days (min – max)	98 – 98	35 – 654	42 – 539
Probability of remaining in response after 12 months, % (95% CI)	N/R	40.5 (17.7, 62.3)	55.6 (30.5, 74.8)
AP-CML, T315I			
N	2	2	5
Patients who lost MaHR, n (%)	1 (50)	1 (50)	2 (40)
Patients maintaining MaHR, n (%)	1 (50)	1 (50)	3 (60)
Median, days (95% CI)	NR	NR	NR
Range, days (min – max)	42 – 309	52 – 598	49 – 436
Probability of remaining in response after 12 months, % (95% CI)	N/R	50 (0.6, 91.0)	60 (12.6, 88.2)

Source: AP24534-10-201 Table 14.2.6.12.2.2. Data extraction date 09 November 2012.
Note: The median of the duration of response and 95% confidence intervals are calculated using the Kaplan-Meier method. Patients who did not demonstrate progression or loss of response were censored at the last response assessment date.
CML=chronic myeloid leukemia, CP=chronic phase, MCyR=major cytogenetic response, R/I=resistant or intolerant, N/A=not available, NR=not reached, CI=confidence interval, min=minimum, max=maximum.

Table 30: Duration of MaHR by Number of Prior Approved TKIs: BP-CML patients in AP24534-10- 201: Treated population

	BP-CML/Ph+ ALL		
	1 TKI (N=9)	2 TKIs (N=37)	3 TKIs (N=48)
BP-CML/Ph+ ALL, R/I			
N	1	7	9
Patients who lost MaHR, n (%)	1 (100)	4 (57.1)	6 (66.7)
Patients maintaining MaHR, n (%)	0 (0)	3 (42.9)	3 (33.3)
Median, days (95% CI)	196 (N/A, N/A)	456 (62, N/A)	98 (54, N/A)
Range, days (min – max)	196 – 196	62 – 597	54 – 485
Probability of remaining in response after 12 months, % (95% CI)	NR	53.6 (13.2, 82.5)	33.3 (7.8, 62.3)
BP-CML/Ph+ ALL, T315I			
N	2	8	5
Patients who lost MaHR, n (%)	2 (100)	5 (62.5)	5 (100)
Patients maintaining MaHR, n (%)	0 (0)	3 (37.5)	0 (0)
Median, days (95% CI)	84 (70, 98)	126 (56, N/A)	105 (54, 143)
Range, days (min – max)	70 – 98	30 – 418	54 – 143
Probability of remaining in response after 12 months, % (95% CI)	NR	17.1 (0.8, 52.6)	NR

Source: AP24534-10-201 Table 14.2.6.12.2.2. Data extraction date 09 November 2012.
Note: The median of the duration of response and 95% confidence intervals are calculated using the Kaplan-Meier method. Patients who did not demonstrate progression or loss of response were censored at the last response assessment date.
CML=chronic myeloid leukemia, CP=chronic phase, MCyR=major cytogenetic response, R/I=resistant or intolerant, N/A=not available, NR=not reached, CI=confidence interval, min=minimum, max=maximum.

Table 31: Duration of MCyR by Number of Prior Approved TKIs: AP-CML patients in AP24534-10- 201: Treated population

	AP-CML		
	1 TKI (N=4)	2 TKIs (N=33)	3 TKIs (N=46)
AP-CML, R/I			
N	1	9	12
Patients who lost MCyR, n (%)	0 (0)	3 (33.3)	2 (16.7)
Patients maintaining MCyR, n (%)	1 (100)	6 (66.7)	10 (83.3)
Median, days (95% CI)	NR	NR	NR
Range, days (min – max)	108 – 108	26 – 394	1 – 421
Probability of remaining in response after 12 months, % (95% CI)	NR	66.7 (28.2, 87.8)	80.8 (42.3, 94.9)
AP-CML, T315I			
N	3	4	3
Patients who lost MCyR, n (%)	1 (33.3)	0 (0)	2 (66.7)
Patients maintaining MCyR, n (%)	2 (66.7)	4 (100)	1 (33.3)
Median, days (95% CI)	NR	NR	NR
Range, days (min – max)	115 – 239	281 – 505	28 – 321
Probability of remaining in response after 12 months, %	NR	100	NR

Source: AP24534-10-201 Table 14.2.6.12.1.2. Data extraction date 09 November 2012.
Note: The median of the duration of response and 95% confidence intervals are calculated using the Kaplan-Meier method. Patients who did not demonstrate progression or loss of response were censored at the last response assessment date.
CML=chronic myeloid leukemia, CP=chronic phase, MCyR=major cytogenetic response, R/I=resistant or intolerant, N/A=not available, NR=not reached, CI=confidence interval, min=minimum, max=maximum.

Table 32: Duration of MCyR by Number of Prior Approved TKIs: BP-CML/Ph+ ALL patients in AP24534-10-201: Treated population

	BP-CML/Ph+ ALL		
	1 TKI (N=9)	2 TKIs (N=37)	3 TKIs (N=48)
BP-CML/Ph+ ALL, R/I			
N	1	6	6
Patients who lost MCyR, n (%)	0 (0)	1 (16.7)	1 (16.7)
Patients maintaining MCyR, n (%)	1 (100)	5 (83.3)	5 (83.3)
Median, days (95% CI)	NR	NR	NR
Range, days (min – max)	421 – 421	1 – 590	27 – 491
Probability of remaining in response after 12 months, % (95% CI)	100	80 (20.4, 96.9)	100
BP-CML/Ph+ ALL, T315I			
N	4	9	3
Patients who lost MCyR, n (%)	3 (75)	6 (66.7)	0 (0)
Patients maintaining MCyR, n (%)	1 (25)	3 (33.3)	3 (100)
Median, days (95% CI)	29 (21, 63)	50 (27, 137)	NR
Range, days (min – max)	1 – 63	1 – 393	30 – 106
Probability of remaining in response after 12 months, %	NR	14.3 (0.7, 46.5)	NR

Source: AP24534-10-201 Table 14.2.6.12.1.2. Data extraction date 09 November 2012.
Note: The median of the duration of response and 95% confidence intervals are calculated using the Kaplan-Meier method. Patients who did not demonstrate progression or loss of response were censored at the last response assessment date.
CML=chronic myeloid leukemia, CP=chronic phase, MCyR=major cytogenetic response, R/I=resistant or intolerant, N/A=not available, N/R=not reached, CI=confidence interval, min=minimum, max=maximum.

Response and duration of response (MCyR and MMR in CP patients, and MaHR and MCyR in more advanced patients) in patients subjected to dose decrement in the 201 study: These data and results are summarised in the tables below.

Table 33: Best response to therapy in AP24534-10-201: Patients with dose reductions

	CP-CML			AP-CML			BP-CML, Ph+ ALL		
	Total N=177	Cohort A CP/R-I N=142	Cohort B CP/T315I N=35	Total N=48	Cohort C AP/R-I N=41	Cohort D AP/T315I N=7	Total BP-CML, Ph+ ALL N=21	Cohort E BP, Ph+ ALL/R-I N=14	Cohort F BP, Ph+ ALL/ T315I N=7
Hematologic, n (%)									
CHR	172 (97.2)	138 (97.2)	34 (97.1)	N/A	N/A	N/A	N/A	N/A	N/A
MaHR	N/A	N/A	N/A	31 (64.6)	27 (65.9)	4 (57.1)	14 (66.7)	10 (71.4)	4 (57.1)
Cytogenetic, n (%)									
MCyR	98 (55.4)	71 (50.0)	27 (77.1)	17 (35.4)	14 (34.1)	3 (42.9)	13 (61.9)	7 (50.0)	6 (85.7)
CCyR	78 (44.1)	54 (38.0)	24 (68.6)	12 (25.0)	10 (24.4)	2 (28.6)	10 (47.6)	6 (42.9)	4 (57.1)
PCyR	20 (11.3)	17 (12.0)	3 (8.6)	5 (10.4)	4 (9.8)	1 (14.3)	3 (14.3)	1 (7.1)	2 (28.6)
Molecular, n (%)									
MMR[a]	55 (31.1)	34 (23.9)	21 (60.0)	5 (10.4)	4 (9.8)	1 (14.3)	5 (23.8)	4 (28.6)	1 (14.3)

Source: AP24534-10-201 Table 14.2.4.1.2.2 (Cytogenetic and hematologic), Table 14.2.7.1.3 (MMR). Data extraction date 09 November 2012.

CP-CML= chronic phase chronic myeloid leukemia, AP-CML= accelerated phase chronic myeloid leukemia, BP-CML= blast phase chronic myeloid leukemia, Ph+ ALL =acute lymphocytic leukemia, N/A = Not applicable.

a. Patients for whom a valid baseline MMR assessment is missing or who meet criteria for MMR at baseline are analyzed as nonresponders.

Table 34: Best response to therapy in AP24534-10-201: Patients with dose interruptions, reductions or both

	CP-CML			AP-CML			BP-CML, Ph+ ALL		
	Total N=215	Cohort A CP/R-I N=164	Cohort B CP/T315I N=51	Total N=63	Cohort C AP/R-I N=50	Cohort D AP/T315I N=13	Total BP-CML, Ph+ ALL N=42	Cohort E BP, Ph+ ALL/R-I N=27	Cohort F BP, Ph+ ALL/ T315I N=15
Hematologic, n (%)									
CHR	207 (96.3)	160 (97.6)	47 (92.2)	N/A	N/A	N/A	N/A	N/A	N/A
MaHR	N/A	N/A	N/A	39 (61.9)	32 (64.0)	7 (53.8)	21 (50.0)	12 (44.4)	9 (60.0)
Cytogenetic, n (%)									
MCyR	123 (57.2)	87 (53.0)	36 (70.6)	24 (38.1)	17 (34.0)	7 (53.8)	16 (38.1)	9 (33.3)	7 (46.7)
CCyR	99 (46.0)	66 (40.2)	33 (64.7)	15 (23.8)	11 (22.0)	4 (30.8)	13 (31.0)	8 (29.6)	5 (33.3)
PCyR	24 (11.2)	21 (12.8)	3 (5.9)	9 (14.3)	6 (12.0)	3 (23.1)	3 (7.1)	1 (3.7)	2 (13.3)
Molecular, n (%)									
MMR[a]	72 (33.5)	43 (26.2)	29 (56.9)	8 (12.7)	5 (10.0)	3 (23.1)	8 (19.0)	6 (22.2)	2 (13.3)

Source: AP24534-10-201 Table 14.2.4.1.2.3 (Cytogenetic and hematologic), Table 14.2.7.1.4 (MMR). Data extraction date 09 November 2012.

CP-CML= chronic phase chronic myeloid leukemia, AP-CML= accelerated phase chronic myeloid leukemia, BP-CML= blast phase chronic myeloid leukemia, Ph+ ALL =acute lymphocytic leukemia, N/A = Not applicable.

a. Patients for whom a valid baseline MMR assessment is missing or who meet criteria for MMR at baseline are analyzed as nonresponders.

Note: A dose interruption was defined as a gap of at least 3 days between non-missing doses.

Table 35: Duration of response CP-CML in AP24534-10-201: Patients with dose reductions

	CP-CML		
	Overall N=177	R/I N=142	T351I N=35
Cytogenetic Response			
Duration of MCyR			
N	98	71	27
Patients who lost MCyR, n (%)	7 (7.1)	7 (9.9)	0
Patients who maintained MCyR, n (%)	91 (92.9)	64 (90.1)	27 (100)
Median, days (95% CI)	NR	NR	NR
Range, days (min – max)	1 – 591	1 – 591	1 – 590
Probability of remaining in response after 6 months, %, (95% CI)	91.7 (83.3, 96.0)	88.3 (77.0, 94.3)	100
Probability of remaining in response after 12 months, % (95% CI)	91.7 (83.3, 96.0)	88.3 (77.0, 94.3)	100
Molecular Response			
Duration of MMR			
N	55	34	21
Patients who lost MMR, n (%)	10 (18.2)	8 (23.5)	2 (9.5)
Patients who maintained MMR, n (%)	45 (81.8)	26 (76.5)	19 (90.5)
Median, days (95% CI)	NR	NR	NR
Range, days (min – max)	1 – 590	1 – 589	1 – 590
Probability of remaining in response after 6 months, %	83.3 (69.3, 91.3)	80.1 (60.9, 90.6)	88.9 (62.4, 97.1)
Probability of remaining in response after 12 months, %	77.9 (62.5, 87.6)	71.9 (51.2, 85.0)	88.9 (62.4, 97.1)

Source: AP24534-10-201 Table 14.2.5.1.1.1, Table 14.2.5.1.3.1. Data extraction date: 09 November 2012.
Note: The median of the duration of response and 95% confidence intervals are calculated using the Kaplan-Meier method. Patients who did not demonstrate progression or loss of response were censored at the last response assessment date.
CML=chronic myeloid leukemia, CP=chronic phase, CHR=complete hematologic response, MCyR=major cytogenetic response, MMR= major molecular response, R/I=resistant or intolerant, N/A=not available, N/R=not reached, CI=confidence interval, min=minimum, max=maximum.

Table 36: Duration of response AP-CML in AP24534-10-201: Patients with dose reductions

	AP-CML		
	Overall N=48	R/I N=41	T351I N=7
Hematologic Response			
Duration of MaHR			
N	31	27	4
Patients who lost MaHR, n (%)	18 (58.1)	16 (59.3)	2 (50.0)
Patients who maintained MaHR, n (%)	13 (41.9)	11 (40.7)	2 (50.0)
Median, days (95% CI)	272 (210, -)	272 (210, -)	NR
Range, days (min – max)	42 – 654	42 – 654	49 – 332
Probability of remaining in response after 6 months, %	73.5 (53.9, 85.8)	77 (55.9, 89.0)	50.0 (5.8, 84.5)
Probability of remaining in response after 12 months, %	38.5 (19.5, 57.2)	37.4 (17.8, 57.0)	-
Cytogenetic Response			
Duration of MCyR			
N	17	14	3
Patients who lost MCyR, n (%)	5 (29.4)	4 (28.6)	1 (33.3)
Patients who maintained MCyR, n (%)	12 (70.6)	10 (71.4)	2 (66.7)
Median, days (95% CI)	NR	NR	NR
Range, days (min – max)	1 – 421	1 – 421	28 – 321
Probability of remaining in response after 6 months, %	68.2 (39.5, 85.4)	68.4 (35.9, 86.8)	66.7 (5.4, 94.5)
Probability of remaining in response after 12 months, %	68.2 (39.5, 85.4)	68.4 (35.9, 86.8)	-

Source: AP24534-10-201 Table 14.2.5.1.1.1, Table 14.2.5.1.2.1. Data extraction date: 09 November 2012.
Note: The median of the duration of response and 95% confidence intervals are calculated using the Kaplan-Meier method. Patients who did not demonstrate progression or loss of response were censored at the last response assessment date.
CML=chronic myeloid leukemia, AP=accelerated phase, MaHR=major hematologic response, MCyR=major cytogenetic response, MMR=major molecular response, R/I=resistant or intolerant, N/A=not available, N/R=not reached, CI=confidence interval, min=minimum, max=maximum.

Table 37: Duration of response BP-CML/Ph+ ALL in AP24534-10-201: Patients with dose reductions

	BP-CML/Ph+ ALL		
	Overall N=21	R/I N=14	T351I N=7
Hematologic Response			
Duration of MaHR			
N	14	10	4
Patients who lost MaHR, n (%)	6 (42.9)	4 (40.0)	2 (50.0)
Patients who maintained MaHR, n (%)	8 (57.1)	6 (60.0)	2 (50.0)
Median, days (95% CI)	NR	NR	108 (82, -)
Range, days (min – max)	56 – 597	56 – 597	63 – 418
Probability of remaining in response after 6 months, %	69.6 (37.8, 87.4)	80.0 (40.9, 94.6)	33.3 (0.9, 77.4)
Probability of remaining in response after 12 months, %	53.1 (23.6, 75.7)	58.3 (23.0, 82.1)	33.3 (0.9, 77.4)
Cytogenetic Response			
Duration of MCyR			
N	13	7	6
Patients who lost MCyR, n (%)	3 (23.1)	0	3 (50.0)
Patients who maintained MCyR, n (%)	10 (76.9)	7 (100)	3 (50.0)
Median, days (95% CI)	NR	NR	137 (29.0, -)
Range, days (min – max)	1 – 590	1 – 590	1 – 393
Probability of remaining in response after 6 months, %	70.7 (33.7, 89.5)	100	26.7 (1.0, 68.6)
Probability of remaining in response after 12 months, %	70.7 (33.7, 89.5)	100	26.7 (1.0, 68.6)

Source: AP24534-10-201 Table 14.2.5.1.1.1, Table 14.2.5.1.2.1. Data extraction date: 09 November 2012.
Note: The median of the duration of response and 95% confidence intervals were calculated using the Kaplan-Meier method. Patients who did not demonstrate progression or loss of response were censored at the last response assessment date.
CML=chronic myeloid leukemia, BP=blast phase, Ph+=Philadelphia chromosome-positive, ALL=acute lymphoid leukemia, MCyR=major cytogenetic response, MMR=major molecular response, R/I=resistant or intolerant, N/A=not available, N/R=not reached, CI=confidence interval, min=minimum, max=maximum.

Table 38: Duration of response CP-CML in AP24534-10-201: Patients with dose interruptions, reductions, or both

	CP-CML		
	Overall N=215	R/I N=164	T351I N=51
Cytogenetic Response			
Duration of MCyR			
N	123	87	36
Patients who lost MCyR, n (%)	10 (8.1)	10 (11.5)	0
Patients who maintained MCyR, n (%)	113 (91.9)	77 (88.5)	36 (100)
Median, days (95% CI)	NR	NR	NR
Range, days (min – max)	1, 591	1, 591	1, 590
Probability of remaining in response after 6 months, %, (95% CI)	90.7 (83.3, 94.9)	86.7 (76.7, 92.6)	100
Probability of remaining in response after 12 months, % (95% CI)	90.7 (83.3, 94.9)	86.7 (76.7, 92.6)	100
Molecular Response			
Duration of MMR			
N	72	43	29
Patients who lost MMR, n (%)	13 (18.1)	9 (20.9)	4 (13.8)
Patients who maintained MMR, n (%)	59 (81.9)	34 (79.1)	25 (86.2)
Median, days (95% CI)	NR	NR	NR
Range, days (min – max)	1, 590	1, 589	1, 590
Probability of remaining in response after 6 months, %	82.3 (70.3, 89.8)	81.2 (64.6, 90.6)	84.0 (62.8, 93.7)
Probability of remaining in response after 12 months, %	78.2 (65.2, 86.8)	74.8 (57.0, 86.1)	84.0 (62.8, 93.7)

Source: AP24534-10-201 Table 14.2.5.1.1.3, Table 14.2.5.1.3.3. Data extraction date: 09 November 2012.
Note: The median of the duration of response and 95% confidence intervals are calculated using the Kaplan-Meier method. Patients who did not demonstrate progression or loss of response were censored at the last response assessment date.
CML=chronic myeloid leukemia, CP=chronic phase, CHR=complete hematologic response, MCyR=major cytogenetic response, MMR= major molecular response, R/I=resistant or intolerant, N/A=not available, N/R=not reached, CI=confidence interval, min=minimum, max=maximum.

Table 39: Duration of response AP-CML in AP24534-10-201: Patients with dose interruptions, reductions, or both

	AP-CML		
	Overall N=63	R/I N=50	T351I N=13
Hematologic Response			
Duration of MaHR			
N	39	32	7
Patients who lost MaHR, n (%)	21 (53.8)	18 (56.3)	3 (42.9)
Patients who maintained MaHR, n (%)	18 (46.2)	14 (43.8)	4 (57.1)
Median, days (95% CI)	289 (210.0, -)	289.0 (210.0, -)	NR
Range, days (min – max)	35, 654	35, 654	42, 598
Probability of remaining in response after 6 months, %	71.3 (54.2, 83.0)	74.4 (55.3, 86.3)	57.1 (17.2, 83.7)
Probability of remaining in response after 12 months, %	44.7 (27.5, 60.5)	42.2 (23.7, 59.5)	57.1 (17.2, 83.7)
Cytogenetic Response			
Duration of MCyR			
N	24	17	7
Patients who lost MCyR, n (%)	7 (29.2)	4 (23.5)	3 (42.9)
Patients who maintained MCyR, n (%)	17 (70.8)	13 (76.5)	4 (57.1)
Median, days (95% CI)	NR	NR	NR
Range, days (min – max)	1, 505	1, 421	28, 505
Probability of remaining in response after 6 months, %	68.5 (44.9, 83.6)	74.5 (45.4, 89.6)	53.6 (13.2, 82.5)
Probability of remaining in response after 12 months, %	68.5 (44.9, 83.6)	74.5 (45.5, 89.6)	53.6 (13.2, 82.5)

Source: AP24534-10-201 Table 14.2.5.1.1.3, Table 14.2.5.1.2.3. Data extraction date: 09 November 2012.
Note: The median of the duration of response and 95% confidence intervals are calculated using the Kaplan-Meier method. Patients who did not demonstrate progression or loss of response were censored at the last response assessment date.
CML=chronic myeloid leukemia, AP=accelerated phase, MaHR=major hematologic response, MCyR=major cytogenetic response, MMR=major molecular response, R/I=resistant or intolerant, N/A=not available, N/R=not reached, CI=confidence interval, min=minimum, max=maximum.

Progression-free Survival Kaplan-Meier curves were prepared for CP-CML, AP-CML and BP-CML/Ph+ ALL. At the time of analyses, the median follow-up, especially for CP-CML and AP-CML patients, was too limited to allow for meaningful conclusions from these data. A brief summary of the preliminary analysis to date (median follow-up 9.9 months) has been provided by the applicant.

For CP-CML all patients combined, as well as individual cohorts R/I (Cohort A) and T315I (Cohort B), the median PFS has not yet been reached. For the overall CP-CML group (n=267), the probability of maintaining PFS at week 26 and week 52 is estimated as 91.0% and 79.6%, respectively. For the R/I and T315I cohorts, the probability of maintaining PFS at week 26 is estimated as 91.6% and 89.3%, respectively; and, the probability of maintaining PFS at week 52 is estimated as 77.7% and 86.7%, respectively.

For the overall AP-CML group (n=83), the median PFS is estimated as 79.9 weeks (range 6.0 to 80.0 weeks), and the probability of maintaining PFS at week 26 and week 52 is estimated as 80.1% and 56.9%, respectively (Figure 11-8). For the R/I and T315I cohorts, the probability of maintaining PFS at week 26 is estimated as 80.9% and 77.4%, respectively; and, the probability of maintaining PFS at week 52 is estimated as 54.7% and 64.5%, respectively.

The natural history of treated BP-CML and Ph+ ALL is marked by more rapid progression; therefore, the data for these cohorts are more conclusive. For the overall BP-CML/Ph+ ALL group (n=94), the median

PFS is estimated as 17.9 weeks (range 0.1 to 64.1 weeks), and the probability of maintaining PFS at week 26 and week 52 is estimated as 34.4% and 19.7%, respectively. For the R/I and T315I cohorts, the probability of maintaining PFS at week 26 is estimated as 34.4% and 19.7%, respectively.

Overall survival (OS) Kaplan-Meier curves were prepared for CP-CML, AP-CML and BP-CML/Ph+ ALL.

For CP-CML all patients combined, as well as individual cohorts R/I (Cohort A) and T315I (Cohort B), the median OS has not yet been reached. For the overall CP-CML group (n=267), the probability of OS at week 26 and week 52 is estimated as 97.3% and 93.5%, respectively. For the R/I and T315I cohorts, the probability of OS at week 26 is estimated as 96.9% and 98.4%, respectively; and, the probability of OS at week 52 is estimated as 94.4% and 90.2%, respectively.

For AP-CML all patients combined, as well as individual cohorts R/I (Cohort C) and T315I (Cohort D), the median OS has not yet been reached. For the overall AP-CML group (n=83), and the probability of OS at week 26 and week 52 is estimated as 96.3% and 82.1%, respectively. For the R/I and T315I cohorts, the probability of OS at week 26 is estimated as 95.4% and 100%, respectively; and, the probability of OS at week 52 is estimated as 83.9% and 72.2%, respectively.

For BP-CML and Ph+ ALL, the prognosis of relapsed disease is severe, and even with the relatively short follow-up available to date, the data are instructive. For the overall BP-CML/Ph+ ALL group (n=94), the median OS is estimated as 29.9 weeks (range 0.4 to 66.0 weeks), and the probability of OS at week 26 and week 52 is estimated as 54.3% and 33.4%, respectively. For the R/I and T315I cohorts, the probability of OS at week 26 is estimated as 53.6% and 55.0%, respectively; and, the probability of OS at week 52 is estimated as 54.3% and 33.4%, respectively.

Ancillary analyses

Molecular genetic analyses were included as an exploratory endpoint. These data are still being investigated as the study in ongoing; however, preliminary results are available including baseline molecular status and response by mutation.

Overall, the most frequent BCR-ABL mutations reported at study entry were T315I (28.5%), F317L (8.0%), E255K (4.0%), and F359V (3.8%).

Cytogenetic and molecular response rates for the most frequent mutations in CP-CML patients were: 74.0% and 50.0% for T315I; 50.0% and 36.4% for F317L; 46.2% and 23.1% for F359V; 62.5% and 50.0% for E255K; and 75.0% and 37.5% for G250E, respectively.

Patients with no detectable BCR-ABL mutations also responded: 46.3% MCyR and 19.1% MMR.

In CP-CML patients, 16 different mutations were detected in ≥2 patients at study entry.

At the time of analysis (median follow-up 9.9 months), for every individual mutation that was detected at least twice at entry (i.e., 16 different mutations) a response was achieved in at least 1 patient.

Patients with no mutations in BCR-ABL also responded: CP-CML- MCyR 46.3% and MMR 19.1%.

Summary of main study

The following tables summarise the efficacy results from the main studies 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 40: Summary of Efficacy for trial AP24534-10-201

Title: A Pivotal Phase 2 Trial of Ponatinib (AP24534) in Patients with Refractory Chronic Myeloid Leukaemia and Ph+ Acute Lymphoblastic Leukaemia			
Study identifier	**AP24534-10-201**		
Design	Multi-centre, international, phase 2, single-arm, open-label trial of oral ponatinib in patients with Ph+ disease, who were either: resistant/intolerant to therapy with dasatinib or nilotinib (R/I cohorts); or had the breakpoint cluster region-Abelson complex (BCR-ABL) T315I mutation.		
	Duration of main phase:		Enrolment into the study was completed on the 04th October 2011. Data from study initiation (21 September 2010) to 02 March 2012 (visit cut-off date), have been presented.
Hypothesis	**Exploratory:** In the first-in-human phase 1 dose-finding study of ponatinib, the agent was well tolerated and demonstrated clinical activity in a heavily pre-treated population of Ph+ patients who were refractory to, or relapsed on, currently available TKIs. The most common treatment-related adverse events were skin disorders and constitutional symptoms, which were manageable. The aim of the study was to examine the efficacy and safety of ponatinib as a potential therapy for these patients. In the phase 1 dose-finding study, ponatinib 45 mg once daily was selected as the recommended dose for investigation in phase 2.		
Treatments groups/ Patient cohorts The starting dose of ponatinib was 45 mg taken orally once daily, the recommended dose determined in the phase 1 study.	**Cohort A (n=203)**		**CP-CML patients, with disease resistant to, or intolerant to dasatinib or nilotinib (R/I)** 100 patients were planned for this cohort. The study recruited 203 patients in this cohort.
	Cohort B (n=64)		**CP-CML patients, with T315I mutation** 60 patients were planned for this cohort. The study recruited 64 patients in this cohort.
	Cohort C (n=65)		**AP-CML patients, with disease resistant to, or intolerant to dasatinib or nilotinib (R/I)** 40 patients were planned for this cohort. The study recruited 65 patients in this cohort.
	Cohort D (n=18)		**AP-CML patients, with T315I mutation** 40 patients were planned for this cohort. The study recruited 18 patients in this cohort.
	Cohort E (n=48)		**BP-CML / Ph+ALL patients, with disease resistant to, or intolerant to dasatinib or nilotinib (R/I)** 40 patients were planned for this cohort. The study recruited 48 patients in this cohort.
	Cohort F (n=46)		**BP-CML / Ph+ALL patients, with T315I mutation** 40 patients were planned for this cohort. The study recruited 46 patients in this cohort.
	Other		5 patients recruited, out of the total 449, had a history of T315I that was not confirmed by mutation testing at study entry, and did not have prior therapy with either dasatinib or nilotinib; therefore, they were not eligible for any cohort in the study.
Endpoints and definitions	**Primary endpoint**	**Cohorts A-B**	Major Cytogenetic response (MCyR)

		Cohorts C-F	Major Hematologic response (MaHR)
	Secondary endpoints	**Cohorts A-B**	Proportion of patients who achieved: Complete Hematologic response (CHR); MCyR; and major molecular response (MMR)
		Cohorts C-F	MCyR and MMR
		All cohorts	Time to response, duration of response, progression-free survival, and overall survival.
		All cohorts	Safety and tolerability
Database cutoff	27^{th} April 2012		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	The "safety population" (N=449) included all patients who received at least 1 dose of study drug. The "treated population" (N=444) included all patients assigned to Cohorts A through F who received at least 1 dose of study drug. There were 267 CP-CML patients (R/I Cohort A: n=203, T315I Cohort B: n=64), 83 AP-CML patients (R/I Cohort C: n=65, T315I Cohort D: n=18), and 94 BP-CML/Ph+ ALL patients (R/I Cohort E: n=48, T315I Cohort F: n=46) in the treated population. **The results presented below are those observed with the treated population.** At the time of analysis (27 April 2012), 252 patients (56.1%) were ongoing, mostly CP-CML (n=185) or AP-CML (n=56).

Descriptive statistics and estimate variability: CP-CML population	**CP-CML**	**Cohort A CP-CML (R/I)**	**Cohort B CP-CML (T315I)**	**Total CP-CML**
	Number of subjects (N)	203	64	267
	MCyR (n/N; %)	99/203 (48.8%)	45/64 (70.3%)	144/267 (53.9%)
	95% CI	41.7-55.9	57.6- 81.1	47.8- 60.0
	CHR (n/N; %)	191/203 (94.1%)	58/64 (94.1%)	249/267 (93.3%)
	95% CI	89.9-96.9	80.7-96.5	89.6- 96.0
	MMR (n/N; %)	47/203 (23.2%)	32/64 (50%)	79/267 (29.6%)
	95% CI	17.5- 29.6	37.2- 62.8	24.2- 35.5
Descriptive statistics and estimate variability: AP-CML population	**AP-CML**	**Cohort C AP-CML (R/I)**	**Cohort D AP-CML (T315I)**	**Total AP-CML**

	Number of subjects (N)	65	18	83
	MaHR (n/N; %)	39/65 (60%)	9/18 (50%)	48/83 (57.8%)
	95% CI	47.1-72.0	26.0- 74.0	46.5- 68.6
	MCyR (n/N; %)	22/65 (33.8%)	10/18 (55.6%)	32/83 (38.6%)
	95% CI			
	MMR (n/N; %)	6/65 (9.2%)	3/18 (16.7%)	9/83 (10.8%)
	95% CI	3.5-19.0	3.6- 41.4	5.1- 19.6
Descriptive statistics and estimate variability: BP-CML / Ph+ ALL population	**BP-CML/ Ph+ALL**	**Cohort E BP-CML/ Ph+ALL (R/I)**	**Cohort F BP-CML/ Ph+ALL (T315I)**	**Total BP-CML/ Ph+ALL**
	Number of subjects (N)	48	46	94
	MaHR (n/N; %)	17/48 (35.4%)	15/46 (32.6%)	32/94 (34%)
	95% CI	22.2- 50.5	19.5- 48.0	24.6- 44.5
	MMR (n/N)	9/48 (18.8%)	2/46 (4.3%)	11/94 (11.7%)
	95% CI	8.9- 32.6	0.5- 14.8	6.0- 20.0
Descriptive statistics and estimate variability: BP-CML separately	**BP-CML**	**BP-CML (R/I)**	**BP-CML (T315I)**	**Total BP-CML**
	Number of subjects (N)	38	24	62
	MaHR (n/N; %)	12/38 (31.6%)	7/24 (29.2%)	19/62 (30.6%)
	95% CI	17.5%- 48.7%	12.6%- 51.1%	19.6%- 43.7%
	MCyR (n/N)	7/38 (18.4%)	7/24 (34.8%)	29/94 (30.9%)
	95% CI			
	MMR (n/N)	7/38 (18.4%)	1/24 (4.2%)	8/62 (12.9%)
	95% CI			
Descriptive statistics and estimate variability: Ph+ ALL separately	**Ph+ ALL**	**Ph+ ALL (R/I)**	**Ph+ ALL (T315I)**	**Total Ph+ ALL**
	Number of subjects (N)	10	22	32
	MaHR (n/N; %)	5/10 (50%)	8/22 (36.4%)	13/32 (40.6%)
	95% CI	18.7%- 81.3%	17.2%- 59.3%	23.7%- 59.4%
	MCyR (n/N)	6/10 (60%)	9/22 (40.9%)	15/32 (46.9%)
	MMR (n/N)	2/10 (20%)	1/22 (4.5%)	3/32 (9.4%)

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

Ponatinib Phase 1 and Phase 2 Studies: Best Response								
Disease Stage	**Phase 1 (Ph+ Patients)[a, b]**				**Phase 2**			
	MCyR	**MaHR**	**CHR**	**MMR**	**MCyR[c]**	**MaHR[d]**	**CHR[d]**	**MMR[e]**
CP-CML								
Overall	31/43 (72.1)	N/A	42/43 (97.7)	19/43 (44.2)	144/267 (53.9)	N/A	249/267 (93.3)	79/267 (29.6)
R/I	20/31 (64.5)	N/A	30/31 (96.8)	11/31 (35.5)	99/203 (48.8)	N/A	191/203 (94.1)	47/203 (23.2)
T315I	11/12 (91.7)	N/A	12/12 (100.0)	8/12 (66.7)	45/64 (70.3)	N/A	58/64 (90.6)	32/64 (50.0)
AP-CML								
Overall	2/9 (22.2)	4/9 (44.4)	N/A	1/9 (11.1)	32/83 (38.6)	48/83 (57.8)	N/A	9/83 (10.8)
R/I	2/8 (25)	4/8 (50)	N/A	0/8	22/65 (33.8)	39/65 (60.0)	N/A	6/65 (9.2)
T315I	0/1	0/1	N/A	1/1	10/18 (55.6)	9/18 (50.0)	N/A	3/18 (16.7)
BP-CML/Ph+ ALL								
Overall	5/13 (38.5)	4/13 (30.8)	N/A	1/13 (7.7)	29/94 (30.9)	32/94 (34.0)	N/A	11/94 (11.7)
R/I	3/7 (42.8)	2/7 (28.6)	N/A	0/7	13/48 (27.1)	17/48 (35.4)	N/A	9/48 (18.8)
T315I	2/6 (33.3)	2/6 (33.3)	N/A	1/6 (16.7)	16/46 (34.8)	15/46 (32.6)	N/A	2/46 (4.3)

Data cut-off date: Phase 1 = 23 March 2012

a In the phase 1 study, all treated patients were included in the analysis of response. Response rates presented are maintained or achieved response while on study. In CP-CML, 26 patients entered in CHR, and remained in CHR. One patient had CCyR at baseline, maintained CCyR on study after entering the study in molecular relapse, then achieved MMR on study. One patient had PCyR at baseline and maintained PCyR on study. In AP-CML, 2 patients entered the study in MaHR.

b R/I in the phase 1 study is defined in parallel with the phase 2 study as patients being relapsed or refractory, but not carrying the T315I mutation.

Data cut-off date: Phase 2 = 27 April 2012

c Patients entering the trial in PCyR must achieve a CCyR in order to be considered as meeting the criteria for MCyR.

d In the analysis of hematologic response, patients for whom baseline bone marrow blasts could not be determined were analysed as non-responders. CP-CML patients who entered the trial in CHR and continued to meet criteria for CHR on study were analysed as responders. Patients with advanced phase disease who entered the trial in MaHR were analysed as non-responders.

e Patients for whom a valid baseline MMR assessment was missing or who meet the criteria for MMR at baseline were analysed as non-responders.

Supportive study

The dose finding study AP24534-07-101 contains endpoints supportive of the efficacy (see also section 2.5.1).

Enrolled patients had advanced haematological malignancies (e.g., leukaemia, multiple myeloma), including CML that had relapsed, or was refractory to standard chemotherapy or approved TKIs, or for which no standard therapy was available. Overall, 65 patients had Ph+ leukaemia. These included 60 CML (43 CP-CML, 9 AP-CML and 8 BP-CML) and 5 Ph+ ALL.

Of the 65 Ph+ patients, 18 (27.7%) had no mutations at study entry, 37 (56.9%) had 1 mutation, 5 (7.7%) had 2 mutations, and 5 (7.7%) had no sequencing data. The most frequent BCR-ABL mutations reported at study entry were T315I (29.2%), F317L (10.8%), and G250E (6.2%).

This patient population was characterised by haematologic malignancy that was refractory or resistant to available therapy or for which no therapies were available. Ph+ patients were heavily treated with prior TKIs and conventional therapies. The most frequently reported prior cancer treatments in CP-CML patients included approved TKIs, imatinib, dasatinib, and nilotinib, as well as hydroxyurea, interferon,

cytarabine, and omacetaxine. Only 1 CP-CML patient had a prior SCT, as well as 1 patient each with BP-CML and Ph+ ALL.

At the time of analysis, out of the 65 Ph+ patients, 42 (64.6%) had CHR, 38 (58.5%) had MCyR, and 21 (32.3%) had MMR. Of note, molecular responses were deep with 15.4% of patients experiencing MR4 and 4.6% CMR4.5.

Of 43 CP-CML patients, 31 CP-CML patients achieved a MCyR with a median duration of follow-up of 25.3 months (range: 1.7 to 38.4 months). At the time of reporting, 25 CP-CML patients were in MCyR (median duration of MCyR had not been reached).

Table 41: Ponatinib Phase 1 Study: Best Response Ph+ Leukemia

Best Response	Response Rate, n (%)					
	Total Ph+ Patients N=65	CP-CML N=43	AP-CML BP-CML Ph+ALL			
			Total N=22	AP-CML N=9	BP-CML N=8	Ph+ ALL N=5
Hematologic						
CHR	42 (64.6)	42 (97.7)	N/A	N/A	N/A	N/A
MaHR	8 (12.3)	N/A	8 (36.4)	4 (44.4)	2 (25.0)	2 (40.0)
Partial hematologic response	1 (1.5)	0	1 (4.5)	0	1 (12.5)	0
Minor hematologic response	1 (1.5)	0	1 (4.5)	1 (11.1)	0	0
No response/stable disease	5 (7.7)	0	5 (22.7)	1 (11.1)	1 (12.5)	3 (60.0)
Progressive disease	2 (3.1)	0	2 (9.1)	0	2 (25.0)	0
No post-baseline assessment	6 (9.2)	1 (2.3)	5 (22.7)	3 (33.3)	2 (25.0)	0
Cytogenetic						
MCyR	38 (58.5)	31 (72.1)	7 (31.8)	2 (22.2)	3 (37.5)	2 (40.0)
CCyR	32 (49.2)	28 (65.1)	4 (18.2)	2 (22.2)	1 (12.5)	1 (20.0)
PCyR	6 (9.2)	3 (7.0)	3 (13.6)	0	2 (25.0)	1 (20.0)
Minor cytogenetic response	2 (3.1)	2 (4.7)	0	0	0	0
Minimal cytogenetic response	5 (7.7)	4 (9.3)	1 (4.5)	1 (11.1)	0	0
No response	10 (15.4)	5 (11.6)	5 (22.7)	3 (33.3)	0	2 (40.0)
No post-baseline assessment	10 (15.4)	1 (2.3) [b]	9 (40.9) [c]	3 (33.3)	5 (62.5)	1 (20.0)
Molecular						
MMR	21 (32.3)	19 (44.2)	2 (9.1)	1 (11.1)	0	1 (20.0)
MR4	10 (15.4)	10 (23.3)	0	0	0	0
CMR4.5	3 (4.6)	3 (7.0)	0	0	0	0
No major molecular response	35 (53.9)	22 (51.2)	13 (59.1)	5 (55.5)	7 (87.5)	1 (20.0)
No valid baseline or post-baseline assessment	7 (10.8)	1 (2.3)	6 (27.3)	3 (33.3)	1 (12.5)	2 (40.0)
Baseline assessment for e1a2 variant only	2 (3.1)	1 (2.3)	1 (4.5)	0	0	1 (20.0)

Database cut-off date 23 March 2012.
CP=chronic phase, CML=chronic myeloid leukaemia, AP=accelerated phase, BP=blast phase, Ph+ ALL=acute lymphoblastic leukaemia, CHR=complete hematologic response, N/A=Not applicable, MaHR=major hematologic response, MCyR=major cytogenetic response, CCyR=complete cytogenetic response, PCyR=partial cytogenetic response, MMR=major molecular response, MR=molecular response, CMR=complete molecular response.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The application is based on a phase I dose-finding study and an open single-arm phase II study with a total of 6 cohorts; R/I or T315I+ patients with CP-CML, AP-CML, and BP/Ph+ ALL disease, respectively. The limitations of single arm open labelled studies are known. In this case the criteria, when a single arm study might be acceptable, have been previously discussed in the CHMP scientific advice given to the applicant. Design and endpoints were discussed with SAWP and although generally accepted it was concluded that a non-comparative design may not be acceptable for patients resistant or intolerant to a second-line agent without a BCR-ABL mutation and the sponsor was cautioned that results barely meeting the statistical objectives may not support regulatory approval.

It is here noted that the final alternative response rate for the CP-CML R/I cohort was lowered from 40% at the time of the advice to 35%. However, it is important to note that the observed response rates far exceed both these limits.

Efficacy data and additional analyses

In the pivotal phase II study, at a median follow-up of 14.5 months, ponatinib exhibited clinically meaningful responses in all stages of Ph+ leukaemia in this heavily pre-treated patient population, which is consistent with the preliminary findings of the phase 1 study.

At the time of analysis, median duration of Iclusig treatment was 281 days in CP-CML patients, 286 days in AP-CML patients, 89 days in BP-CML patients, and 81 days in patients with Ph+ ALL.

This patient population was characterised by Ph+ leukaemia patients who were resistant or intolerant to prior dasatinib or nilotinib; were heavily pre-treated with prior TKIs and convention therapy; were relatively advanced in their diagnosis (median time since diagnosis was 6.1 years); and 54.8% had BCR-ABL resistance mutations confirmed at entry, including T315I. Overall, the majority of patients were resistant (87.6%); only 11.7% were purely intolerant to prior dasatinib or nilotinib therapy.

Most patients had exhausted available TKI options and conventional therapies, and best response to most recent prior tyrosine kinase inhibitor therapy has been highlighted.

The response rates achieved in each of the 6 study cohorts met the pre-specified statistical criteria for success. For all cohorts, the estimated rate exceeded the pre-specified interesting value.

In CP-CML, 16 different mutations were detected in ≥2 patients at entry; for all 16 of these mutations, there was at least 1 response, which is consistent with the pan-BCR-ABL inhibitor activity of ponatinib observed *in vitro*.

Ponatinib had efficacy in both groups of patients included in the study (i.e., R/I and T315I cohorts).

There were significantly higher response rates in patients who were less heavily treated. All patients who failed prior TKI therapies demonstrated responses, and response rates in CP-CML patients. Of the CP-CML patients previously treated with one, two, or three prior TKIs, 81% (13/16), 61% (65/105), and 46% (66/143) achieved a MCyR while on Iclusig, respectively.

Responses were found to be durable; the median duration of response has not yet been reached for CP-CML patients.

Generally the data shows that, in study 201, the populations with dose reductions or dose interruption or both, did not perform inferior in terms of primary and secondary endpoints or probability of remaining in response of the primary endpoint at 12 months in relation to the corresponding overall population; the exception being AP patients where, overall, 50% with MaHR were estimated to retain their response at 12 months, compared with 39% among AP-CML patients with dose reductions and 45% among patients with reductions/interruptions

It is noted that the MaHR rates and probability of remaining at response at 12 months were superior in the above sub-populations BP/Ph+ ALL compared to the corresponding overall population. This variability could be because of the small numbers of patients with adjustments, or because patients in this disease group who do not continue on therapy with dose adjustments have discontinued due to disease progression.

A post hoc multivariate analysis (data not shown) examining the impact of several predictor variables and outcomes in the CP-CML population in the phase 2 study was performed. Dose intensity and patient age were significant predictors for MCyR in CP-CML patients. The number of prior TKIs and time since

diagnosis trended toward significance. Increasing response rate was therefore correlated with increased dose intensity, younger age, fewer prior therapies, and less time since diagnosis. Notably, T315I mutation status is not an independent predictor of response, despite the higher response rates observed in Cohort B. This may be explained by the significant association between dose intensity and T315I status, and between age and T315I status. The T315I CP-CML patients are younger and tolerate higher doses.

2.5.4. Conclusions on the clinical efficacy

The findings in the pivotal phase 2 study were consistent with, and confirm, the initial activity findings of ponatinib in the phase 1 setting. The magnitude of response rates shown in the two clinical studies is considered clinically relevant, especially for, but not restricted to, CML patients harbouring the T315I mutation. Ponatinib has demonstrated efficacy in heavily pre-treated Ph+ leukaemia patients in all stages of disease, i.e., patients who have received dasatinib/ nilotinib as second line or further line TKI therapy; and in patients with the T315I mutation.

It is noted that, in the pivotal study, there are very few patients without the T315I mutation that received only one line of therapy with either dasatinib or nilotinib. However considering the broader target activity of dasatinib and nilotinib, treatment with imatinib following failure of first line treatment with these agents, is considered inappropriate. Therefore the use of ponatinib would be a viable option, and has been taken into consideration in the wording of the indication.

Another issue to be noted is that nilotinib is not approved for the treatment of Ph+ ALL, although patients with Ph+ ALL pre-treated with nilotinib have been included in the pivotal study. This fact was taken into consideration in the wording of the indication.

2.6. Clinical safety

Patient exposure

Five clinical studies of ponatinib have been conducted and are included in this dossier: 2 in patients and 3 in healthy subjects. In all, 530 patients and 53 healthy subjects have received ponatinib through these studies.

In addition, an expanded access program is providing ponatinib to patients through individual patient treatment INDs in the United States (US); Named Patient Programs (NPPs) in Europe, Australia, Canada, and Singapore; and an expanded access protocol in the US (AP24534-12-901). As of 03 June 2012, 212 patients have been approved to receive ponatinib through the INDs and NPPs. As of 28 June 2012, 18 patients have enrolled at 3 sites in the expanded access protocol.

Finally, 2 investigator-sponsored trials (ISTs) are underway with 14 patients enrolled according to updates received as of 01 July 2012: "Phase II Study of Combination of Hyper-CVAD and Ponatinib in Patients With Philadelphia (PH) Chromosome Positive and/or BCR-ABL Positive Acute Lymphoblastic Leukaemia (ALL)" being conducted by Dr. Susan O'Brien (M.D. Anderson Cancer Centre, Houston, Texas, United States); and "Ponatinib as Initial Therapy for Patients With Chronic Myeloid Leukaemia in Chronic Phase" being conducted by Dr. Jorge Cortes (M.D. Anderson Cancer Centre, Houston, Texas, United States).

Safety results from the 3 healthy-subject studies and SAEs from the expanded access program and ISTs have been discussed briefly by the applicant. The main discussion provided was the description of the safety results from each of the 2 studies in patients and a display and discussion of safety analyses from

the pooled data from these 2 studies. Unless otherwise stated, the data that follow are from the pooled safety population, from these 2 studies.

Table 42: Patient exposure in phase I study AP24534-07-101 (data cut-off 23 March 2012), and phase II study AP24534-10-201(data cut-off date 27 April 2012)

	Overall Total N=530[a] n (%)	CP-CML			AP-CML			BP-CML/Ph+ ALL		
		Total N=313[b] n (%)	R/I N=231 n (%)	T315I N=76 n (%)	Total N=94[b] n (%)	R/I N=73 n (%)	T315I N=19 n (%)	Total N=107[b] n (%)	R/I N=54 n (%)	T315I N=52 n (%)
Ongoing	285 (53.8)	216 (69.0)	154 (66.7)	57 (75.0)	58 (61.7)	46 (63.0)	10 (52.6)	11 (10.3)	9 (16.7)	2 (3.8)
Discontinued	245 (46.2)	97 (31.0)	77 (33.3)	19 (25.0)	36 (38.3)	27 (37.0)	9 (47.4)	96 (89.7)	45 (83.3)	50 (96.2)
Primary Reason for Discontinuation[c]										
Progressive disease	93 (17.5)	21 (6.7)	14 (6.1)	7 (9.2)	14 (14.9)	9 (12.3)	5 (26.3)	54 (50.5)	26 (48.1)	28 (53.8)
Adverse event	63 (11.9)	36 (11.5)	32 (13.9)	4 (5.3)	12 (12.8)	9 (12.3)	3 (15.8)	11 (10.3)	5 (9.3)	5 (9.6)
Death	26 (4.9)	5 (1.6)	3 (1.3)	2 (2.6)	3 (3.2)	2 (2.7)	1 (5.3)	13 (12.1)	7 (13.0)	6 (11.5)
Consent withdrawn/ Withdrawal by subject	19 (3.6)	15 (4.8)	14 (6.1)	1 (1.3)	1 (1.1)	1 (1.4)	0	3 (2.8)	1 (1.9)	2 (3.8)
Physician decision/ Administrative decision	19 (3.6)	9 (2.9)	6 (2.6)	2 (2.6)	2 (2.1)	2 (2.7)	0	5 (4.7)	2 (3.7)	3 (5.8)
Lack of efficacy	11 (2.1)	6 (1.9)	6 (2.6)	0	1 (1.1)	1 (1.4)	0	4 (3.7)	1 (1.9)	3 (5.8)
Noncompliance with study drug	1 (0.2)	1 (0.3)	1 (0.4)	0	0	0	0	0	0	0
Other	13 (2.5)	4 (1.3)	1 (0.4)	3 (3.9)	3 (3.2)	3 (4.1)	0	6 (5.6)	3 (5.6)	3 (5.8)

Source: Appendix Table 1, Table 2.1, Table 2.2, Table 2.3. Data cut-off dates: 23 Mar 2012 for AP24534-07-101 and 27 Apr 2012 for AP24534-10-201.

a Includes 16 patients from AP24534-07-101 with other diseases (AML, MDS, MM, MS).

b Includes 6 patients in CP-CML, 2 patients in AP-CML, and 1 patient in BP-CML/Ph+ ALL disease groups who failed to meet criteria for either cohort category.

c Possible primary reasons for treatment discontinuation in both studies include: adverse event, death, noncompliance with study drug, (documented) progressive disease, and lost to follow-up. Additional possible reasons in the phase 1 study include: consent withdrawn and administrative decision. Additional possible reasons in the phase 2 study include: lack of efficacy, physician decision, pregnancy, study terminated by sponsor, withdrawal by subject, and other. Reasons not shown above had an overall n of 0.

Abbreviations: AE= Adverse event, ALL = Acute lymphoblastic leukaemia, AP = accelerated phase, BP = blast phase, CML = Chronic myeloid leukaemia, CP = chronic phase, n = number of patients, Ph+ = Philadelphia chromosome, R/I = resistant or intolerant to dasatinib or nilotinib, T315I = having the T315I mutation.

Table 43: Overall Extent of Exposure: Safety Population by Disease Group and Cohort

	Overall	CP-CML			AP-CML			BP-CML/Ph+ ALL		
	N=530[a]	Total N=313[b]	R/I N=231	T315I N=76	Total N=94[b]	R/I N=73	T315I N=19	Total N=107[b]	R/I N=54	T315I N=52
Observed Total Dose (mg)										
Mean (SD)	8426.6 (7167.4)	10000.4 (7639.4)	9254.4 (7303.0)	11915.9 (8203.0)	8707.3 (6694.5)	8064.3 (6708.1)	10402.6 (6366.4)	4544.3 (3961.8)	5201.8 (4503.4)	3907.8 (3250.2)
Median	6937.5	8805.0	8250.0	9997.5	7140.0	5235.0	9810.0	3420.0	4050.0	3037.5
Range (Min-Max)	45-53340	135-53340	135-53340	945-45300	60-32921	60-32921	495-23220	45-16605	45-16605	104-15210
Dose Intensity (mg/day)										

	Overall	CP-CML			AP-CML			BP-CML/Ph+ ALL		
	N=530[a]	Total N=313[b]	R/I N=231	T315I N=76	Total N=94[b]	R/I N=73	T315I N=19	Total N=107[b]	R/I N=54	T315I N=52
Mean (SD)	33.0 (12.8)	31.7 (11.9)	30.4 (12.2)	35.6 (10.1)	29.8 (14.4)	28.1 (14.6)	35.3 (12.8)	39.8 (10.2)	39.0 (10.2)	40.5 (10.3)
Median	36.1	31.4	30.2	37.0	33.6	28.8	40.5	44.1	42.6	44.9
Range (Min-Max)	2-60	4-60	4-59	13-60	2-45	2-45	7-45	2-60	8-60	2-60
Relative Dose Intensity, % (Total Dose/Expected Total Dose[c] [× 100%])										
Mean (SD)	75.4 (26.1)	71.3 (25.7)	68.5 (26.5)	79.5 (21.2)	69.6 (30.4)	66.2 (31.4)	80.9 (24.5)	89.9 (16.6)	87.5 (18.5)	92.6 (14.3)
Median	84.6	71.0	68.3	87.2	80.0	68.3	89.9	98.0	95.6	99.7
Range (Min-Max)	8-115	8-100	8-100	25-100	11-100	11-100	17-100	33-115	33-100	45-115
Duration of Exposure (days)										
Mean (SD)	265.5 (195.2)	318.8 (199.1)	306.9 (187.5)	340.8 (219.0)	287.7 (168.9)	287.8 (181.2)	273.3 (117.2)	120.0 (109.6)	144.8 (131.2)	95.8 (75.5)
Median	264.5	303.0	304.0	283.5	285.0	286.0	258.0	84.0	91.5	71.0
Range (Min-Max)	1-1151	3-1151	3-1099	27-1151	3-1017	3-1017	66-542	1-449	1-449	3-338
Number (%) of patients treated for…										
<1 month	35 (6.6)	14 (4.5)	13 (5.6)	1 (1.3)	3 (3.2)	3 (4.1)	0	13 (12.1)	6 (11.1)	7 (13.5)
1 to <3 mos	78 (14.7)	17 (5.4)	13 (5.6)	4 (5.3)	6 (6.4)	5 (6.8)	1 (5.3)	48 (44.9)	21 (38.9)	26 (50.0)
3 to <6 mos	71 (13.4)	31 (9.9)	22 (9.5)	9 (11.8)	15 (16.0)	12 (16.4)	3 (15.8)	21 (19.6)	12 (22.2)	9 (17.3)
6 to <12 mos	247 (46.6)	178 (56.9)	133 (57.6)	42 (55.3)	49 (52.1)	38 (52.1)	11 (57.9)	20 (18.7)	10 (18.5)	10 (19.2)
12 to <24 mos	79 (14.9)	56 (17.9)	41 (17.7)	14 (18.4)	18 (19.1)	12 (16.4)	4 (21.1)	5 (4.7)	5 (9.3)	0
≥24 mos	20 (3.8)	17 (5.4)	9 (3.9)	6 (7.9)	3 (3.2)	3 (4.1)	0	0	NA	NA
Dose modifications (% of patients with at least one…)										
Interruption[f]	342 (64.5)	234 (74.8)	176 (76.2)	54 (71.1)	61 (64.9)	48 (65.8)	12 (63.2)	42 (39.3)	26 (48.1)	16 (30.8)
Reduction	268 (50.6)	195 (62.3)	150 (64.9)	41 (53.9)	51 (54.3)	42 (57.5)	8 (42.1)	20 (18.7)	12 (22.2)	7 (13.5)
Total Person Years[g]	428.81	298.89	213.09	77.16	81.77	63.51	15.78	43.95	25.84	17.91

Source: Appendix Table 122, Table 123.1, Table 123.2, Table 123.3, Table 132, Table 133.1, Table 133.2, and Table 133.3. Data cut-off dates: 23 Mar 2012 for AP24534-07-101 and 27 Apr 2012 for AP24534-10-201.

a Includes 16 patients from AP24534-07-101 with other diseases (AML, MDS, MM, MS).

b Includes 6 patients in CP-CML, 2 patients in AP-CML, and 1 patient in BP-CML/Ph+ ALL disease groups who failed to meet criteria for either cohort category.

c Expected Total Dose for phase 2: 45 mg multiplied by the number of days on study; for phase 1: patients' initial dose level for those who did not receive a dose escalation, and latest escalated dose for those who did receive a dose escalation.

d Expected Days Dosed is defined as the number of days between first dose and last dose.

e Dose intensity is calculated as total mg received/days on study treatment.

f Dose interruption is defined as a gap of at least 3 days between non-missing doses.

g Total Person Years are calculated as duration of exposure + 30 days × number of patients/365.25

Abbreviations: ALL = Acute lymphoblastic leukaemia, AP = accelerated phase, BP = blast phase, CML = Chronic myeloid leukaemia, CP = chronic phase, Min = minimum, Max = maximum, mos = months, N and n = number of patients, Ph+ = Philadelphia chromosome, R/I= Resistant or intolerant to dasatinib or nilotinib, SD = standard deviation, T315I = having the T315I mutation, TKI = tyrosine kinase inhibitor.

Adverse events

Table 43: Treatment-related treatment-emergent adverse events (Study AP24534-10-201; frequency reported by incidence of TEAEs)

MedDRA SOC/PT	Total
Number of Patients With at Least One Adverse Event	446 (99.3%)
GASTROINTESTINAL DISORDERS	
ABDOMINAL PAIN	159 (35.4%)
CONSTIPATION	145 (32.3%)
NAUSEA	105 (23.4%)
DIARRHOEA	76 (16.9%)
VOMITING	76 (16.9%)
DRY MOUTH	29 (6.5%)
PANCREATITIS	27 (6.0%)

ABDOMINAL DISTENSION	25 (5.6%)
DYSPEPSIA	17 (3.8%)
STOMATITIS	17 (3.8%)
GASTROOESOPHAGEAL REFLUX DISEASE	16 (3.6%)
ABDOMINAL DISCOMFORT	13 (2.9%)
GASTRIC HAEMORRHAGE	1 (0.2%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
RASH	163 (36.3%)
DRY SKIN	147 (32.7%)
ERYTHEMA	34 (7.6%)
PRURITUS	32 (7.1%)
RASH PRURITIC	30 (6.7%)
ALOPECIA	27 (6.0%)
NIGHT SWEATS	26 (5.8%)
SKIN EXFOLIATION	22 (4.9%)
HYPERHIDROSIS	18 (4.0%)
EXFOLIATIVE RASH	13 (2.9%)
PETECHIAE	13 (2.9%)
ECCHYMOSIS	9 (2.0%)
PAIN OF SKIN	7 (1.6%)
PERIORBITAL OEDEMA	7 (1.6%)
DERMATITIS EXFOLIATIVE	4 (0.9%)
INVESTIGATIONS	
PLATELET COUNT DECREASED	179 (39.9%)
NEUTROPHIL COUNT DECREASED	104 (23.2%)
LIPASE INCREASED	79 (17.6%)
ALANINE AMINOTRANSFERASE INCREASED	51 (11.4%)
ASPARTATE AMINOTRANSFERASE INCREASED	43 (9.6%)
WEIGHT DECREASED	27 (6.0%)
BLOOD AMYLASE INCREASED	23 (5.1%)
BLOOD ALKALINE PHOSPHATASE INCREASED	19 (4.2%)
WHITE BLOOD CELL COUNT DECREASED	19 (4.2%)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	18 (4.0%)
BLOOD BILIRUBIN INCREASED	13 (2.9%)
EJECTION FRACTION DECREASED	12 (2.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
FATIGUE	117 (26.1%)
PYREXIA	111 (24.7%)
ASTHENIA	55 (12.2%)
OEDEMA PERIPHERAL	52 (11.6%)
PAIN	40 (8.9%)
CHILLS	39 (8.7%)
NON-CARDIAC CHEST PAIN	18 (4.0%)
INFLUENZA LIKE ILLNESS	14 (3.1%)
MASS	6 (1.3%)
FACE OEDEMA	5 (1.1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
ARTHRALGIA	110 (24.5%)
MYALGIA	85 (18.9%)
PAIN IN EXTREMITY	65 (14.5%)
BACK PAIN	61 (13.6%)
BONE PAIN	52 (11.6%)
MUSCLE SPASMS	42 (9.4%)
MUSCULOSKELETAL PAIN	34 (7.6%)
NECK PAIN	15 (3.3%)
MUSCULOSKELETAL CHEST PAIN	9 (2.0%)
NERVOUS SYSTEM DISORDERS	
HEADACHE	148 (33.0%)
DIZZINESS	35 (7.8%)
LETHARGY	13 (2.9%)
PARAESTHESIA	13 (2.9%)
NEUROPATHY PERIPHERAL	11 (2.4%)
HYPOAESTHESIA	8 (1.8%)
MIGRAINE	8 (1.8%)
HYPERAESTHESIA	5 (1.1%)
CEREBRAL INFARCTION	2 (0.4%)
CEREBRAL ARTERY STENOSIS	1 (0.2%)
INFECTIONS AND INFESTATIONS	
UPPER RESPIRATORY TRACT INFECTION	40 (8.9%)
PNEUMONIA	27 (6.0%)
FOLLICULITIS	12 (2.7%)
SEPSIS	11 (2.4%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
COUGH	57 (12.7%)
DYSPNOEA	50 (11.1%)
PLEURAL EFFUSION	29 (6.5%)
EPISTAXIS	27 (6.0%)
DYSPHONIA	19 (4.2%)
PULMONARY EMBOLISM	4 (0.9%)
METABOLISM AND NUTRITION DISORDERS	

DECREASED APPETITE	46 (10.2%)
HYPOKALAEMIA	29 (6.5%)
HYPERURICAEMIA	26 (5.8%)
HYPOCALCAEMIA	24 (5.3%)
HYPOPHOSPHATAEMIA	17 (3.8%)
HYPERGLYCAEMIA	15 (3.3%)
DEHYDRATION	13 (2.9%)
HYPERTRIGLYCERIDAEMIA	8 (1.8%)
FLUID RETENTION	5 (1.1%)
TUMOUR LYSIS SYNDROME	3 (0.7%)
VASCULAR DISORDERS	
HYPERTENSION	81 (18.0%)
HOT FLUSH	14 (3.1%)
FLUSHING	9 (2.0%)
DEEP VEIN THROMBOSIS	6 (1.3%)
EMBOLISM VENOUS	1 (0.2%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
ANAEMIA	87 (19.4%)
FEBRILE NEUTROPENIA	20 (4.5%)
PANCYTOPENIA	9 (2.0%)
EYE DISORDERS	
DRY EYE	25 (5.6%)
VISION BLURRED	12 (2.7%)
EYELID OEDEMA	3 (0.7%)
RETINAL VEIN THROMBOSIS	1 (0.2%)
CARDIAC DISORDERS	
ATRIAL FIBRILLATION	17 (3.8%)
PERICARDIAL EFFUSION	13 (2.9%)
CARDIAC FAILURE CONGESTIVE	10 (2.2%)
ANGINA PECTORIS	9 (2.0%)
CARDIAC FAILURE	8 (1.8%)
MYOCARDIAL INFARCTION	8 (1.8%)
CORONARY ARTERY DISEASE	7 (1.6%)
ATRIAL FLUTTER	4 (0.9%)
LEFT VENTRICULAR DYSFUNCTION	1 (0.2%)
PSYCHIATRIC DISORDERS	
INSOMNIA	34 (7.6%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	
ERECTILE DYSFUNCTION	13 (2.9%)
HEPATOBILIARY DISORDERS	
HEPATOTOXICITY	3 (0.7%)
JAUNDICE	1 (0.2%)

Table 44: Treatment-Emergent Adverse Events by System Organ Class in Safety Population (N=530): Of Any Grade in ≥10% or with Incidence of Grade ≥3 in ≥2% of Patients

System Organ Class Preferred Term	**Any grade** **n (%)**	**Grade 3** **n (%)**	**Grade 4** **n (%)**	**Grade 5** **n (%)**
No. of Patients with ≥1 AE, n (%)	**527 (99.4)**	**218 (41.1)**	**139 (26.2)**	**78 (14.7)**
Infections and infestations	**290 (54.7)**	**76 (14.3)**	**12 (2.3)**	**15 (2.8)**
Upper respiratory tract infection	54 (10.2)	3 (0.6)	0	0
Pneumonia	40 (7.5)	24 (4.5)	4 (0.8)	4 (0.8)
Sepsis	14 (2.6)	7 (1.3)	4 (0.8)	3 (0.6)
Neoplasms benign, malignant, and unspecified	**78 (14.7)**	**12 (2.3)**	**5 (0.9)**	**37 (7.0)**
Neoplasm progression	41 (7.7)	2 (0.4)	4 (0.8)	34 (6.4)
Blood and lymphatic system disorders	**155 (29.2)**	**80 (15.1)**	**19 (3.6)**	**3 (0.6)**
Anaemia	106 (20.0)	60 (11.3)	9 (1.7)	0
Febrile neutropenia	39 (7.4)	29 (5.5)	5 (0.9)	0
Metabolism and nutrition disorders	**208 (39.2)**	**47 (8.9)**	**13 (2.5)**	**1 (0.2)**
Decreased appetite	58 (10.9)	2 (0.4)	0	0
Hypokalaemia	45 (8.5)	11 (2.1)	0	0
Hyponatraemia	22 (4.2)	11 (2.1)	1 (0.2)	0
Nervous system disorders	**286 (54.0)**	**33 (6.2)**	**9 (1.7)**	**7 (1.3)**
Headache	179 (33.8)	11 (2.1)	0	0
Dizziness	53 (10.0)	1 (0.2)	0	0
Vascular disorders	**169 (31.9)**	**51 (9.6)**	**5 (0.9)**	**1 (0.2)**
Hypertension	106 (20.0)	29 (5.5)	2 (0.4)	0
Respiratory, thoracic, and mediastinal disorders	**242 (45.7)**	**31 (5.8)**	**8 (1.5)**	**2 (0.4)**
Cough	73 (13.8)	0	0	0

System Organ Class Preferred Term	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Dyspnoea	64 (12.1)	12 (2.3)	0	0
Gastrointestinal disorders	**412 (77.7)**	**95 (17.9)**	**3 (0.6)**	**1 (0.2)**
Abdominal pain	192 (36.2)	41 (7.7)	0	0
Constipation	178 (33.6)	9 (1.7)	0	0
Nausea	140 (26.4)	4 (0.8)	0	0
Vomiting	105 (19.8)	6 (1.1)	0	0
Diarrhoea	98 (18.5)	6 (1.1)	1 (0.2)	0
Pancreatitis	39 (7.4)	27 (5.1)	0	0
Skin and subcutaneous tissue disorders	**391 (73.8)**	**48 (9.1)**	**1 (0.2)**	**0**
Rash	205 (38.7)	21 (4.0)	0	0
Dry skin	164 (30.9)	7 (1.3)	0	0
Musculoskeletal and connective tissue disorders	**351 (66.2)**	**39 (7.4)**	**0**	**0**
Arthralgia	141 (26.6)	10 (1.9)	0	0
Myalgia	99 (18.7)	3 (0.6)	0	0
Pain in extremity	83 (15.7)	7 (1.3)	0	0
Back pain	76 (14.3)	4 (0.8)	0	0
Bone pain	64 (12.1)	7 (1.3)	0	0
Muscle spasms	61 (11.5)	1 (0.2)	0	0
General disorders and administration site conditions	**359 (67.7)**	**43 (8.1)**	**1 (0.2)**	**6 (1.1)**
Fatigue	153 (28.9)	12 (2.3)	0	0
Pyrexia	138 (26.0)	9 (1.7)	1 (0.2)	2 (0.4)
Oedema peripheral	78 (14.7)	2 (0.4)	0	0
Asthenia	61 (11.5)	11 (2.1)	0	0
Chills	58 (10.9)	2 (0.4)	0	0
Investigations	**367 (69.2)**	**145 (27.4)**	**137 (25.8)**	**0**
Platelet count decreased	206 (38.9)	63 (11.9)	104 (19.6)	0
Neutrophil count decreased	119 (22.5)	59 (11.1)	45 (8.5)	0
Lipase increased	92 (17.4)	45 (8.5)	10 (1.9)	0
Alanine aminotransferase increased	66 (12.5)	24 (4.5)	1 (0.2)	0
Aspartate aminotransferase increased	58 (10.9)	16 (3.0)	1 (0.2)	0
Amylase increased	26 (4.9)	10 (1.9)	1 (0.2)	0
White blood cell count decreased	24 (4.5)	9 (1.7)	5 (0.9)	0

Source: Appendix Table 6. Data cut-off dates: 23 Mar 2012 for AP24534-07-101 and 27 Apr 2012 for AP24534-10-201.

Note: Adverse events are coded using MedDRA v 15.0 and graded according to NCI CTCAE v 3.0 for AP24534-07-101 and CTCAE v 4.03 for AP24534-10-201. Only treatment-emergent adverse events with a start date on or after the first dose of study drug are reported. For patients who experience the same coded event more than once at each level of summarization, the greatest NCI-CTCAE grade is presented. System organ classes are included only if they contain preferred terms meeting the cut-off defined in the table title. Clinically synonymous terms have been recoded to single MedDRA preferred terms.

AE = Adverse event, n = number of patients, No. = number.

Adverse events that occurred in at least 20% of patients were decreased platelet count, rash, abdominal pain, headache, constipation, dry skin, fatigue, arthralgia, nausea, pyrexia, decreased neutrophil count, hypertension, and anaemia.

Adverse events that reached grade ≥3 in >10% of patients overall were decreased platelet count, decreased neutrophil count, anaemia, and increased lipase.

Pancreatitis, which was identified in the phase 1 study as the DLT, occurred in 39 patients (7.4%), with 27 patients' pancreatitis reaching grade 3 (5.1%; no grade 4).

Most adverse events occurred with similar incidence across disease groups; however, a few differences of note were seen. Decreased platelet count occurred in fewer patients with BP-CML/Ph+ ALL (26.2%) than in patients with CP-CML or AP-CML (41.9% and 46.8%, respectively).

A lower percentage of patients with CP-CML (18.2%) reported decreased neutrophil count than patients with the advanced phases (AP-CML: 28.7%; BP-CML/Ph+ ALL: 29.9%). Similarly, febrile neutropenia

increased with increasing disease severity (CP-CML: 1.9%; AP-CML: 4.3%; BP-CML/Ph+ ALL: 20.6%). The percentage of patients with anaemia increased with increasing disease severity (CP-CML: 13.7%; AP-CML: 27.7%; BP-CML/Ph+ ALL: 29.9%).

These results are consistent with those seen in the 2 studies individually.

There are certain adverse events of interest that have been discussed by the applicant. These are adverse events that are either common with ponatinib or known to occur with this class of TKIs. These include myelosuppression and related events, pancreatic events, hepatic events, cardiac events, ischemic vascular events, oedema and fluid retention, and skin and subcutaneous tissue disorders.

Myelosuppression: Myelosuppression was a frequent laboratory finding and reported adverse event in the ponatinib clinical program. A major manifestation of intolerance to prior therapy is also myelosuppression, either due to the interaction between underlying disease and the treatment, or induced by the treatment itself.

Infections were reported in over half of patients. Infections, like myelosuppressive events, are a characteristic feature of the natural history of leukaemia, and they are predisposed by either disease-related or iatrogenic bone marrow depletion. In this program, in most patients the infections were non-serious upper respiratory tract infections, nasopharyngitis, and urinary tract infections. Serious infections were reported in approximately 19% of patients with most of these patients experiencing pneumonia/lung infection and sepsis (including neutropenic sepsis and bacteraemia), typically due to organisms associated with hospital acquired infections. Opportunistic infections (OI) were reported in only 1.3% of patients. Of the patients with an OI, most had been on treatment for <4 months, had advanced disease (AP-CML, BP-CML, Ph+ ALL, and AML) or severe neutropenia at baseline. Approximately 3% of patients had a fatal infection, all of whom had either advanced disease and/or low neutrophil counts. Gram-negative sepsis and/or pneumonia was the most common cause of fatal infection; opportunistic infections (e.g., systemic zygomycosis, fungal pneumonia (not otherwise specified), and Pneumocystis pneumonia) were reported in a few patients with fatal infection.

Bleeding events were commonly reported, with 25% of patients experiencing at least one event. In most patients, however the event was classified as either grade 1 or 2. The most commonly reported preferred terms were epistaxis (6.6% of patients), petechiae (4.2% of patients), and ecchymoses (2.8% of patients). Serious bleeding events were reported in 4.9% of patients. The incidence of serious bleeding events was higher in patients with AP-CML (8.5%) and BP-CML/Ph+ ALL (10.3%) compared to those with CP-CML (1.3%). Cerebral haemorrhage and gastrointestinal haemorrhage were the most commonly reported serious bleeding events, as well as the most commonly reported fatal bleeding events. Fatal bleeding events were reported in 1.3% of patients.

Pancreatic Events: Reversible pancreatitis with pancreatic enzyme abnormality was the DLT from the phase 1 study. Overall in the pooled safety populations of Studies 101 and 201, 129 patients (24.3%) had pancreatic events. These events reached grade 3 or 4 severity for 78 patients (14.7%); no events were fatal (grade 5). The most commonly reported pancreatic events were increased lipase (17.4% of patients; grade 3 or 4: 10.4%), pancreatitis (7.4%; grade 3 or 4: 5.1%), increased amylase (4.9%; grade 3 or 4: 2.1%), and increased blood bilirubin (3.0%; grade 3 or 4: 0.9%). Increased lipase and increased amylase were often accompanied by pancreatitis. Overall, 36 patients (6.8%) had pancreatic related serious adverse events.

The phase 1 protocol allowed no dose modifications for grade 1 or 2 toxicities attributable to study drug, unless the event was intolerable and not controlled by optimal supportive care. Grade 3 or 4 toxicities attributed to study drug could be managed by a combination of dose reduction to one level lower and dose delay of up to 2 weeks. Dose re-escalation was allowed upon agreement with the sponsor's medical

monitor if the patient had recovered and would benefit from the escalated dose. The phase 2 protocol similarly restricted dose modifications to grade 3 or 4 events but had specific guidelines for pancreatic toxicities. Namely, for grade 2 pancreatitis with mild symptoms or radiologic findings, ponatinib was to be held until resolution by imaging, and then resumed at the current dose. For grade 3 pancreatitis, ponatinib was to be withheld and upon resolution restarted at one dose level lower. For grade 3 or 4 amylase or lipase elevations, ponatinib was withheld, and if (or once) imaging was negative or showed resolution, the dose was resumed at the next-lower level (i.e., 45 to 30; 30 to 15 mg).

Of the 35 patients with pancreatic SAEs, 1 had study drug permanently withdrawn, 2 had no action taken, 1 had a dose reduction, and 31 had study drug temporarily discontinued at least once.

Hepatic Events: Overall, 138 patients (26.0%) had at least one adverse event from the SMQ (standardised MedRA Query) for hepatotoxicity; 55 (10.4%) had events that reached grade 3 or 4 in severity. No hepatic adverse events had a fatal (grade 5) outcome.

14 patients (2.6%) were identified as having SAEs in the hepatotoxicity SMQ. Based on liver enzyme levels and other assessments concurrent with some of the SAEs, 8 of these 14 patients did not appear to have SAEs of hepatotoxicity. The remaining 6 patients did have hepatotoxicity SAEs while on study treatment. Study drug was interrupted for all 6 cases. Study drug was restarted for 4 patients and did not restart for 2 patients (1 due to disease progression; and 1 due to physician's decision). The events recurred for 3 patients after restarting study drug. Outcomes were favourable, and all 6 patients recovered from serious hepatotoxic events.

Possible Hy's Law cases (patients at increased risk of drug-induced liver failure as outlined are defined as patients with ALT or AST >3 × ULN, with ALP <2 × ULN and total bilirubin (TBL) ≥2 × ULN with no other aetiology to explain these liver-function test results. There were 2 patients who at a single time point met all the laboratory criteria for Hy's Law cases. These patients both had confounding underlying conditions.

Cardiac Events:

Approved BCR-ABL inhibitors are associated with congestive failure/left ventricular dysfunction (Glivec) and conduction abnormalities (QT prolongation) (dasatinib; nilotinib).

The most commonly reported adverse event term in the **congestive failure/left ventricular dysfunction** (CF/LVD) query was the nonspecific event of oedema peripheral (14.7%). Serious CF/LVD events were reported in 4% of patients with cardiac failure congestive reported in 1.5% of patients, cardiac failure in 0.9% of patients and ejection fraction decreased in 0.9% of patients

Rate and Rhythm Disorders- The most commonly reported arrhythmia was tachycardia with 4.5 %. Most of these events were non-serious and assessed as grade 1 or 2. The second most commonly reported arrhythmia was atrial fibrillation (4.3%), followed by electrocardiogram QT prolonged (2.5%), and palpitations (2.1%). All other arrhythmia events were reported at an incidence of approximately 1% or less.

The AE of **QT prolongation** was reported in 13 patients (2.5%). Of the 13 patients, 7 patients were from AP24534-07-101 in which centralized ECG monitoring in triplicate and pharmacokinetic data were collected. The other 6 patients with an AE of QT prolongation were from Study AP24534-10-201 in which no centralized ECG monitoring was performed.

Of these 6 patients, one patient had a QTcF increase 48 ms above baseline.

Of the remaining 5 patients, 1 had an increase of unreported duration, and 4 had an increase in QTcF of >60 msec from baseline.

Although investigators considered 4 of the 5 cases to be treatment-related, an analysis of each case shows that based on either negative rechallenge with study treatment or resolution of the event with continued dosing these events were most likely not related to ponatinib. One patient had not received any ponatinib for 1 week prior to event onset. Given the half-life of ponatinib and the fact that restart of ponatinib did not lead to recurrence, the event was unlikely related to study drug. One patient, who had a prior history of prolonged QT, developed an increase in QTcF of 82 msec above baseline. Ponatinib was temporarily discontinued and restarted with no recurrence of the event. Two patients developed a prolonged QT that resolved and did not recur, despite continuation of their dosing regimen. One patient, with a history of AV node block, right bundle branch block, and a pacemaker, developed QT prolongation. Although a final outcome was not reported, ponatinib was continued for another 3 weeks, suggesting that the event was probably not related to study treatment.

Cardiac arrest, syncope, and ventricular events: Patients who experienced a cardiac arrest, ventricular event, or serious syncopal event were reviewed and nearly all of the patients had pre-existing cardiac disease, infection, or severe dehydration. None of the patients developed QT-prolongation during the study.

Ischemic Vascular Events: An ischemic vascular event was reported in approximately 11% of patients, and serious ischemic vascular events were reported in 6%. All of the patients with an ischemic event had at least one cardiovascular risk factor and the majority had multiple risk factors (e.g., >65 years of age, male gender, obesity, hypertension, diabetes, and hyperlipidemia).

Most serious ischemic events were cardiovascular in nature with myocardial infarction reported in 2.6% of patients. The observed incidence of coronary ischemic events is possibly explained by the multiple confounding factors in these patients, but the role of ponatinib in the development of these events cannot be determined at this time.

Cerebral infarction was reported in 1.3% of patients, and a serious peripheral ischemic event was reported in <1% of patients. Given the observed incidence of peripheral and cerebrovascular ischemic events in this study, the population demographics, and the individual patient histories, a causal relationship of ponatinib to the development of these conditions appears unlikely.

Fluid retention adverse events were reported in approximately one-quarter of the patients; most patients experienced grade 1 or 2 events (21.2%). The patients who developed serious fluid retention events (2.5%) often had confounding conditions (e.g., pneumonia, congestive cardiac failure, prior dasatinib exposure). Most patients recovered from their SAEs with or without drug interruption within a month.

Skin and Subcutaneous Tissue Disorders were commonly reported, and the majority of the events were non-serious. One patient discontinued due to non-serious exfoliative rash. Seven patients experienced SAEs that were considered related to study drug; all recovered except one patient (who died of sepsis). There were no reports of serious skin toxicity such as Stevens Johnson syndrome or toxic epidermal necrolysis.

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) has been reported with dasatinib. In responses to questions the Applicant presented all cases observed in the ponatinib development programme. These included 11 AEs of PAH, 10 from AP24534-07-101 and AP24534-10-201, and 1 from the expanded access program. Following assessment of these cases it is concluded that there is currently no evidence at the present time to suggest a class effect for ponatinib with regard to pulmonary hypertension. An alternative aetiology or contributory factor for pulmonary hypertension was identified in all 11 cases identified in the

ponatinib development programme and no consistent pattern in the temporal relationship between the start of ponatinib therapy and the onset of pulmonary hypertension was seen. Of the 10 patients whose TKI history was reported, 9 had prior dasatinib, for which an association with pulmonary hypertension has been reported in the medical literature.

Exploratory analyses

An analysis of time periods when patients with advanced disease stages were in complete haematological response and patients with CP-CML had achieved major cytogenetic response, i.e. periods when the adverse events of the disease are expected to be less prominent, showed that the frequency of adverse events reported during these periods were considerably lower than in the overall analysis.

Serious adverse event/deaths/other significant events

Table 45: Serious Treatment-Emergent Adverse Events, Safety Population (N=530): Of any Grade in ≥1% of Patients or with Any Grade 5 Incidence, by Descending Incidence

Preferred Term	Any grade n (%)	Grade 3 and 4 n (%)	Grade 5 n (%)
Neoplasm progression	37 (7.0)	4 (0.8)	32 (6.0)
Pneumonia	31 (5.8)	26 (4.9)	4 (0.8)
Pancreatitis	31 (5.8)	25 (4.7)	0
Febrile neutropenia	25 (4.7)	23 (4.3)	0
Pyrexia	24 (4.5)	4 (0.8)	2 (0.4)
Abdominal pain	20 (3.8)	12 (2.3)	0
Platelet count decreased	17 (3.2)	17 (3.2)	0
Atrial fibrillation	14 (2.6)	6 (1.1)	0
Anaemia	13 (2.5)	10 (1.9)	0
Sepsis	11 (2.1)	8 (1.5)	3 (0.6)
Bacteraemia	8 (1.5)	6 (1.1)	0
Cellulitis	8 (1.5)	7 (1.3)	0
Diarrhoea	8 (1.5)	5 (0.9)	0
Cardiac failure congestive	8 (1.5)	6 (1.1)	2 (0.4)
Myocardial infarction	8 (1.5)	8 (1.5)	0
Hypertension	8 (1.5)	7 (1.3)	0
Neutrophil count decreased	7 (1.3)	7 (1.3)	0
Headache	7 (1.3)	3 (0.6)	0
Dyspnoea	7 (1.3)	3 (0.6)	0
Constipation	6 (1.1)	2 (0.4)	0
Vomiting	6 (1.1)	3 (0.6)	0
Acute myocardial infarction	6 (1.1)	4 (0.8)	1 (0.2)
Pancytopenia	6 (1.1)	6 (1.1)	0
Lipase increased	6 (1.1)	4 (0.8)	0
Dehydration	6 (1.1)	5 (0.9)	1 (0.2)
Hyponatraemia	6 (1.1)	6 (1.1)	0
Septic shock	5 (0.9)	0	5 (0.9)
Cardiac failure	5 (0.9)	4 (0.8)	1 (0.2)
Blast crisis in myelogenous leukaemia	4 (0.8)	1 (0.2)	2 (0.4)
Multi-organ failure	4 (0.8)	0	4 (0.8)
Haemorrhage intracranial	4 (0.8)	0	4 (0.8)
Respiratory failure	4 (0.8)	2 (0.4)	2 (0.4)
Cardiac arrest	3 (0.6)	0	3 (0.6)
Cardiopulmonary failure	2 (0.4)	0	1 (0.2)
Leukocytosis	2 (0.4)	1 (0.2)	1 (0.2)

Preferred Term	Any grade n (%)	Grade 3 and 4 n (%)	Grade 5 n (%)
Enterocolitis infections	1 (0.2)	0	1 (0.2)
Pneumocystis jiroveci pneumonia	1 (0.2)	0	1 (0.2)
Pneumonia fungal	1 (0.2)	0	1 (0.2)
Zygomycosis	1 (0.2)	0	1 (0.2)
Gastritis haemorrhagic	1 (0.2)	0	1 (0.2)
Metastases to meninges	1 (0.2)	0	1 (0.2)
Bone marrow failure	1 (0.2)	0	1 (0.2)
Hyperviscosity syndrome	1 (0.2)	0	1 (0.2)
Brain oedema	1 (0.2)	0	1 (0.2)
Haemorrhagic cerebral infarction	1 (0.2)	0	1 (0.2)
Metabolic encephalopathy	1 (0.2)	0	1 (0.2)
Ischemia	1 (0.2)	0	1 (0.2)

Source: Appendix Table 14. Data cut-off dates: 23 Mar 2012 for AP24534-07-101 and 27 Apr 2012 for AP24534-10-201.

Note: Patients may have more than 1 AE per Preferred Term. At each level of patient summarization, a patient was counted once for the most severe event. AEs were classified according to MedDRA v 15.0 and graded according to NCI CTCAE v 3.0 for AP24534-07-101 and CTCAE v 4.03 for AP24534-10-201. Clinically synonymous terms have been recoded to single MedDRA preferred terms.

Table 46: Serious treatment emergent adverse events by severity, all patients treated with ponatinib in Studies 101 and 201 (N=530)

SOC group	Total SAEs	Grade 3-4	Grade 5 (fatal)
N patients with ≥ 1 SAE	284 (53.6%)	171 (32.3%)	75 (14.2%)
Infections and infestations	99 (18.7%)	73 (13.8%)	15 (2.8%) 4 pneumonia 3 sepsis 5 septic shock 1 enterocolitis infectious 1 pneumocystis jiroveci pneumonia 1pneumonia fungal
Neoplasms benign, malignant and unspecified	55 (10.4%)	14 (2.6%)	35 (6.6%)
Blood and lymphatic system disorders	48 (9.1%)	40 (7.5%)	3 (0.6%) 1 leukocytosis 1 bone marrow failure 1 hyperviscosity syndrome
Immune system disorders	5 (0.9%)	4 (0.8%)	0 (0.0%)
Metabolism and nutrition disorders	19 (3.6%)	16 (3.0%)	1 (0.2%) (1 dehydration
Psychiatric disorders	9 (1.7%)	4 (0.8%)	0 (0.0%)
Nervous system disorders	38 (7.2%)	20 (3.8%)	7 (1.3%) 4 haemorrhage intracranial 1 brain oedema 1 haemorrhagic cerebral infarction 1 metabolic encephalopathy
Eye disorders	2 (0.4%)	1 (0.2%)	0 (0.0%)
Ear and labyrinth disorders	2 (0.4%)	0 (0.0%)	0 (0.0%)
Cardiac disorders	54 (10.2%)	35 (6.6%)	8 (1.5%) 2 cardiac failure congestive 1 acute myocardial infarction 1 cardiac failure 3 cardiac arrest 1 cardiopulmonary failure
Vascular disorders	24 (4.5%)	18 (3.4%)	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	28 (5.3%)	17 (3.2%)	2 (0.4%) 2 respiratory failure
Gastrointestinal disorders	74 (14.0%)	57(10.8%)	1 (0.2%) 1 gastritis haemorrhagic
Hepatobiliary disorders	8 (1.5%)	4 (0.8%)	0 (0.0%)
Skin and subcutaneous	13 (2.5%)	8 (1.5%)	0 (0.0%)

tissue disorders			
Musculoskeletal and connective tissue disorders	14 (2.6%)	9 (1.7%)	0 (0.0%)
Renal and urinary disorders	10 (1.9%)	7 (1.3%)	0 (0.0%)
Reproductive system and breast disorders	3 (0.6%)	1 (0.2%)	0 (0.0%)
General disorders and administration site conditions	43 (8.1%)	14 (2.6%)	6 (1.1%) 2 pyrexia 4 multi-organ failure
Investigations	43 (8.1%)	39 (7.4%)	0 (0.0%)
Injury, poisoning and procedural complications	16 (3.0%)	11 (2.1%)	0 (0.0%)

Table 47: Deaths within 30 Days of the Last Dose of Ponatinib or Any Treatment-Related Deaths: Safety Population

Reason(s) for Death[a]	All pts (N=530) n (%)	CP-CML (N=313) n (%)	AP-CML (N=94) n (%)	BP-CML/ Ph+ ALL (N=107) n (%)	AML/MDS/ MM/MS (N=16) n (%)
Total number of deaths	**66 (12.5)**	**11 (3.5)**	**7 (7.4)**	**41 (38.3)**	**7 (43.8)**
Neoplasm progression	28 (5.3)	4 (1.3)	4 (4.3)	17 (15.9)	3 (18.8)
Septic shock	5 (0.9)	0	1 (1.1)	4 (3.7)	0
Multi-organ failure	4 (0.8)	0	0	2 (1.9)	2 (12.5)
Cardiac arrest	3 (0.6)[b]	2 (0.6)	0	1 (0.9)[b]	0
Haemorrhage intracranial	3 (0.6)	0	0	2 (1.9)	1 (6.3)
Pneumonia	3 (0.6)[b]	2 (0.6)[b]	0	1 (0.9)	0
Blast crisis in myelogenous leukaemia	2 (0.4)	0	0	2 (1.9)	0
Sepsis	2 (0.4)	0	0	2 (1.9)	0
Acute myocardial infarction	1 (0.2)[b]	1 (0.3)[b]	0	0	0
Cardiac failure congestive	1 (0.2)	0	0	1 (0.9)	0
Cardiopulmonary failure	1 (0.2)	0	0	1 (0.9)	0
Dehydration	1 (0.2)	0	0	1 (0.9)	0
Enterocolitis infectious	1 (0.2)	0	0	1 (0.9)	0
Gastritis hemorrhagic	1 (0.2)[b]	0	0	1 (0.9)[b]	0
rrhage intracranial, ycosis, bone marrow failure	1 (0.2)	0	0	1 (0.9)	0
Haemorrhagic cerebral infarction	1 (0.2)	1 (0.3)	0	0	0
Hyperviscosity syndrome	1 (0.2)	0	0	1 (0.9)	0
Ischemia	1 (0.2)	0	0	1 (0.9)	0
Leukocytosis, metabolic encephalopathy	1 (0.2)	0	0	1 (0.9)	0
Metastases to meninges	1 (0.2)	0	1 (1.1)	0	0
Pneumocystis jiroveci pneumonia	1 (0.2)	1 (0.3)	0	0	0
Pneumonia fungal	1 (0.2)[b]	0	1 (1.1)[b]	0	0
Pneumonia, sepsis	1 (0.2)	0	0	0	1 (6.3)
Respiratory failure	1 (0.2)	0	0	1 (0.9)	0

Source: Appendix Table 18.1. Data cut-off dates: 23 Mar 2012 for AP24534-07-101 and 27 Apr 2012 for AP24534-10-201.
a Where investigators listed more than 1 cause of death for a patient, all causes are listed in one row for that patient.
b 1 case considered related to study treatment.

The most common non-disease-progression-related serious adverse events were pneumonia and pancreatitis (5.8% of patients for each).

Fatal (grade 5) serious adverse events included infection-related events (pneumonia, sepsis, septic shock, and pyrexia); cardiac events (congestive cardiac failure, cardiac failure, acute myocardial infarction, cardiac arrest); and bleeding events (intracranial haemorrhage, haemorrhagic gastritis, haemorrhagic cerebral infarction, ischemia).

The overall incidence of serious adverse events by disease group increased with increasing severity of disease (CP-CML: 41.5%; AP-CML: 57.4%; BP-CML/Ph+ ALL: 81.3%). Although individual serious adverse events occurred in few patients, a trend is seen of increasing infection-related serious adverse events with increasing disease severity.

The percentages of patients with the following events in the CP-CML, AP-CML, and BP-CML/Ph+ ALL disease groups, respectively were: pneumonia: 2.6%, 8.5%, 9.3%; febrile neutropenia: 1.0%, 3.2%, 12.1%; and sepsis: 0.6%, 2.1%, 5.6%. These results may be due to the higher incidence of neutropenia seen in the more-advanced disease groups.

These results are consistent with those seen in the 2 studies individually.

Deaths were reported up to the time of the data cut-off for each study. For the purpose of the safety evaluation, the applicant has summarised deaths that occurred within 30 days after the last dose of ponatinib or if they occurred after this window and are considered at least possibly related to study treatment.

Across both studies, 66 patients died within the 30-day window or had a related death more than 30 days after the last dose. The total percentage of patients with deaths in this time frame increased with increasing disease severity, mostly due to disease progression events. Twenty-eight of the deaths (17 in the BP-CML/Ph+ ALL disease group) were due to the neoplasm progression (all unrelated to study treatment).

Of the remaining 38 deaths, 5 (all from AP24534-10-201) were considered at least possibly related to study treatment (1 of these deaths was outside the 30-day time frame).

Laboratory findings

Table 49: Patients with Newly Occurring or Worsening Laboratory Values, Any Grade and Grade 3/4: Safety Population, Overall and by Disease Group

Clinical Laboratory Evaluation	All patients (N=530)[a]		CP-CML (N=313)		AP-CML (N=94)		BP-CML; Ph+ ALL (N=107)	
	Any worsening n (%)	Worsening to grade 3 or 4 n (%)	Any worsening n (%)	Worsening to grade 3 or 4 n (%)	Any worsening n (%)	Worsening to grade 3 or 4 n (%)	Any worsening n (%)	Worsening to grade 3 or 4 n (%)
Haematology								
Thrombocytopenia[b] (platelets decreased)	337 (63.6)	224 (42.3)	199 (63.6)	117 (37.4)	72 (76.6)	45 (47.9)	61 (57.0)	57 (53.3)
Anaemia[b] (Hgb decreased)	287 (54.2)	116 (21.9)	146 (46.6)	30 (9.6)	53 (56.4)	26 (27.7)	77 (72.0)	52 (48.6)
Neutropenia[b] (ANC decreased)	302 (57.0)	190 (35.8)	156 (49.8)	78 (24.9)	70 (74.5)	45 (47.9)	71 (66.4)	62 (57.9)
Lymphopenia	251 (47.4)	110 (20.8)	118 (37.7)	40 (12.8)	56 (59.6)	28 (29.8)	66 (61.7)	32 (29.9)
Leukopenia[b] (WBC decreased)	335 (63.2)	146 (27.5)	177 (56.5)	46 (14.7)	73 (77.7)	32 (34.0)	76 (71.0)	60 (56.1)
Biochemistry								
Albumin decreased	155 (29.2)	5 (0.9)	77 (24.6)	2 (0.6)	26 (27.7)	1 (1.1)	42 (39.3)	2 (1.9)
Alkaline phosphatase increased	188 (35.5)	11 (2.1)	102 (32.6)	3 (1.0)	30 (31.9)	1 (1.1)	48 (44.9)	5 (4.7)
ALT increased	281 (53.0)	42 (7.9)	163 (52.1)	18 (5.8)	53 (56.4)	9 (9.6)	55 (51.4)	14 (13.1)
Amylase increased	13 (2.5)	2 (0.4)	6 (1.9)	0	2 (2.1)	0	4 (3.7)	2 (1.9)
AST increased	214 (40.4)	20 (3.8)	129 (41.2)	10 (3.2)	31 (33.0)	3 (3.2)	45 (42.1)	7 (6.5)
Bicarbonate decreased	53 (10.0)	1 (0.2)	31 (9.9)	1 (0.3)	8 (8.5)	0	14 (13.1)	0
Bilirubin	105 (19.8)	12 (2.3)	45 (14.4)	5 (1.6)	25 (26.6)	3 (3.2)	29 (27.1)	2 (1.9)
Calcium decreased	282 (53.2)	7 (1.3)	163 (52.1)	1 (0.3)	48 (51.1)	1 (1.1)	60 (56.1)	4 (3.7)
Calcium increased	25 (4.7)	2 (0.4)	16 (5.1)	1 (0.3)	5 (5.3)	1 (1.1)	4 (3.7)	0
Creatinine increased	38 (7.2)	1 (0.2)	20 (6.4)	0	3 (3.2)	0	13 (12.1)	1 (0.9)
Glucose decreased[c]	103 (19.4)	0	66 (21.1)	0	24 (25.5)	0	13 (12.1)	0
Glucose increased[c]	252 (47.5)	22 (4.2)	152 (48.6)	15 (4.8)	51 (54.3)	7 (7.4)	49 (45.8)	0
Lipase increased	115 (21.7)	55 (10.4)	76 (24.3)	28 (12.1)	25 (26.6)	9 (9.6)	11 (10.3)	5 (4.7)
Phosphorus decreased	302 (57.0)	43 (8.1)	203 (64.9)	22 (7.0)	50 (53.2)	10 (10.6)	40 (37.4)	9 (8.4)
Potassium decreased	84 (15.8)	9 (1.7)	36 (11.5)	2 (0.6)	22 (23.4)	4 (4.3)	22 (20.6)	2 (1.9)
Potassium increased	82 (15.5)	10 (1.9)	47 (15.0)	6 (1.9)	12 (12.8)	1 (1.1)	17 (15.9)	3 (2.8)
Sodium decreased	160 (30.2)	26 (4.9)	92 (29.4)	15 (4.8)	32 (34.0)	6 (6.4)	29 (27.1)	3 (2.8)
Sodium increased	60 (11.3)	1 (0.2)	41 (13.1)	1 (0.3)	9 (9.6)	0	7 (6.5)	0
Triglycerides	35 (6.6)	4 (0.8)	22 (7.0)	3 (1.0)	4 (4.3)	0	4 (3.7)	1 (0.9)

Clinical Laboratory Evaluation	All patients (N=530)[a]		CP-CML (N=313)		AP-CML (N=94)		BP-CML; Ph+ ALL (N=107)	
	Any worsening n (%)	Worsening to grade 3 or 4 n (%)	Any worsening n (%)	Worsening to grade 3 or 4 n (%)	Any worsening n (%)	Worsening to grade 3 or 4 n (%)	Any worsening n (%)	Worsening to grade 3 or 4 n (%)
increased								

Source: Appendix Table 104. Data cut-off dates: 23 Mar 2012 for AP24534-07-101 and 27 Apr 2012 for AP24534-10-201.
a Includes 16 patients from AP24534-07-101 with other diseases (AML, MDS, MM, MS).
b MedDRA preferred terms corresponding to the hematologic laboratory parameter.
c Glucose was measured in Study AP24534-10-201 only; patients from Study AP24534-07-101 are coded as "unable to evaluate."
Note: Events were graded according to NCI CTCAE v 3.0 for AP24534-07-101 and CTCAE v 4.03 for AP24534-10-201.
chromosome-positive, WBC=white blood cells.

Immunological events

One case of grade 2 hypogammaglobulinemia was reported among the 530 patients in the phase 1 and 2 trials. The patient continued on study drug, with no adverse event of infection. Decreased lymphocyte count was reported in 2% of patients.

Safety in special populations

Gender

The most common adverse events, including decreased platelet count, rash, and headache generally occurred with similar incidences between genders in the patient population overall and by disease group. Pancreatitis also occurred with similar incidence between the groups.

Overall, there was a higher incidence of decreased neutrophil count in women than in men (26.6% vs. 18.8%); this difference held true for CP-CML and AP-CML (CP-CML: 23.0% vs. 13.9%; AP-CML: 39.2% vs. 16.3%), but not for BP-CML/Ph+ ALL (22.5% vs. 34.3%).

Urinary tract infections were seen with higher incidence in women than in men (15.3% versus 1.8%). Other differences were slight, in events that were seen at low incidences, and were not seen consistently across disease groups.

Age

The table below summarises ADRs in the elderly population by age group reported in studies AP24534-07-101 and AP24534-10-201 (N=530)

MedDRA Terms	Age <65 number (percentage) [2]	Age 65-74 number (percentage) [2]	Age 75-84 number (percentage) [2]	Age 85+ number (percentage) [2]
N	**349**	**136**	**39**	**6**
Total ADRs	**311 (89.1)**	**126 (92.6)**	**39 (100)**	**6 (100)**
Serious ADRs – Total	**67 (16.3)**	**39 (28.7)**	**15 (38.5)**	**2 (33.3)**
- Fatal	3 (0.9)	1 (0.7)	1 (2.6)	0
- Hospitalization/prolong existing hospitalization	46 (13.2)	23 (16.9)	11 (28.2)	2 (33.3)
- Life-threatening[a]	1 (1.8)	0	0	0
- Disability/incapacity[a]	0	0	0	0
- Other (medically significant)[a]	1 (1.8)	3 (15.8)	0	0
AE leading to drop-out	19 (5.4)	21 (15.4)	4 (10.3)	0
Psychiatric disorders (SOC)	7 (2.0)	8 (5.9)	4 (10.3)	1 (16.7)
Nervous system disorders (SOC)	92 (26.4)	45 (33.1)	12 (30.8)	1 (16.7)
Accidents and injuries (SMQ)	3 (0.9)	2 (1.5)	1 (2.6)	0
Cardiac disorders (SOC)	15 (4.3)	15 (11.0)	12 (30.8)	1 (16.7)
Vascular disorders (SOC)	31 (8.9)	20 (14.7)	3 (7.7)	0
Cerebrovascular disorders (SMQ)	0	1 (0.7)	0	0
Infections and infestations (SOC)	29 (8.3)	11 (8.1)	5 (12.8)	0
Quality of life decreased (PT)	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	14 (4.0)	4 (2.9)	4 (10.3)	0

Source: Table 169.
a These criteria for seriousness were captured only in the database for AP24534-07-101. Therefore, the percentages for these criteria were obtained using the total number of treated patients in AP24534-07-101 (N=81) as the denominator.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, SMQ = Standardised MedDRA Queries, SOC = System organ class, PT = preferred term

Individual events (any grade) that appear to occur with progressively higher incidence with increasing age included decreased platelet count (37.1%, 34.5%, 42.6%, 51.1%), anaemia (16.9%, 15.8%, 25.0%, 33.3%), peripheral oedema (11.2%, 15.8%, 15.4%, 22.2%), increased lipase (9.6%, 18.1%, 24.3%, 24.4%), dyspnoea (5.1%, 12.9%, 17.6%, 20.0%), asthenia (8.4%, 10.5%, 11.8%, 26.7%), muscle spasms (9.6%, 11.1%, 11.8%, 20.0%), and decreased appetite (7.3%, 8.2%, 15.4%, 22.2%).

Events that occurred with higher incidence in the oldest age group compared with the other groups included pneumonia and pruritus. These trends were generally consistent across disease groups.

Increased alanine aminotransferase and aspartate aminotransferase levels occurred with decreasing incidence from the youngest to oldest age group; this trend was also seen in the CP-CML and BP-CML/Ph+ ALL disease groups.

Febrile neutropenia occurred with the highest incidence in the youngest age group (14.0% versus 3.5% to 4.4%). The trend was not seen in every disease group, possibly because of low overall incidence and low patient numbers in each group.

Overall, a slight increase in the percentage of patients experiencing grade ≥3 events is seen with increasing age. Incidence of Grade 3 increased lipase was higher with increasing age (5.1%, 10.5%, 15.4%, 15.6%), and Grade ≥3 dehydration was highest in the oldest age group (11.1% vs. 0 to 1.8%). Most individual adverse events that reached grade ≥3 occurred with similar incidence across age groups.

An overall trend was seen toward more total serious adverse events in the higher age groups. Though the numbers of patients experiencing these AEs are low, the following observations are made with increasing

age: a higher incidence of serious pneumonia and a lower incidence of serious febrile neutropenia. Abdominal pain and headache were serious in slightly more young patients than old, while the overall incidence of these events (serious and non-serious) was similar across age groups. Cardiac serious adverse events of atrial fibrillation, myocardial infarction, acute myocardial infarction, cardiac arrest, congestive cardiac failure, and cardiac failure occurred with higher incidence in the oldest age groups, as did dehydration and hyponatremia.

Race

Race subgroups collected were the following: American Indian / Alaska Native, Asian, Black or African American, White, Other, and Unknown

Adverse events occurred with similar incidences across race subgroups.

Prior Approved TKIs

The number of patients receiving only 1 prior approved TKI (N=40) was much lower than patients receiving 2 (N=203) or 3 (N=270) prior approved TKIs. Therefore, any differences observed between this group and the others could be due to variability caused by the small population size.

An increase is seen with increasing number of prior TKIs in the percentage of patients with any and with grade ≥3 decreased platelet count. This tendency was also seen in the AP-CML and BP-CML/Ph+ ALL disease groups, but was not as prominent in the CP-CML disease group. Anaemia and lipase increases were slightly more common with increasing prior TKI. Most other events occurred with similar incidence across subgroups.

Time since Diagnosis

Patients were divided into tertiles based on time since diagnosis (0 to <3.2 years; 3.2 to <8.8 years; 8.8 to <28 years). The incidence of most AEs was similar across tertiles. The incidence of decreased platelet count (any grade or grade ≥3) was higher with increasing time since diagnosis. This tendency was also seen in patients with CP-CML and AP-CML, but not in patients with BP-CML/Ph+ ALL. Peripheral oedema, dyspnoea, asthenia, and muscle spasms increased slightly with increasing time since diagnosis; this observation was consistent across disease groups for most of these events. Urinary tract infections, pleural effusion, and pruritus were slightly higher in the longest tertile. Patients with a longer time since diagnosis are also more likely to be older and to have received more treatment regimens than more-recently diagnosed patients.

Safety related to drug-drug interactions and other interactions

Preclinical data suggest that cytochrome P450 3A4 (CYP3A4) is involved in the human metabolism of ponatinib. In the clinical studies in patients, concomitant use of CYP3A4 inhibitors was discouraged, but not prohibited. Therefore, a study was conducted to determine whether concurrent administration of the CYP3A4 inhibitor ketoconazole would inhibit the metabolism of a single dose of ponatinib in healthy subjects (AP24534-11-103).

Concurrent administration of multiple doses of ketoconazole with single-dose ponatinib (15 mg) resulted in a 78% and 47% increase in plasma ponatinib AUC0-∞ and C_{max}, respectively, without affecting time to achieve maximum plasma concentrations. Multiple-dose ketoconazole co-administration also resulted in a 70% decrease in plasma exposure to AP24567 (a metabolite of ponatinib).

Discontinuation due to adverse events

Thirteen patients (16.0%) in the phase 1 study discontinued due to AEs. The 15 events leading to these 13 patients' discontinuations were pancreatitis (2 patients), increased lipase, cardiomyopathy, pyrexia, headache, staphylococcal eye infection, intracranial haemorrhage, graft-versus-host disease, neutropenia (1 patient each), and, in 1 patient, the 3 events of bone pain, febrile neutropenia, and petechiae.

Fifty patients (11.1%) discontinued the phase 2 study due to an AE; an additional 14 patients had progressive disease coded as an AE leading to discontinuation (total summarized in the discontinuation due to AEs = 64). Decreased platelet count (18 patients; 4%) and neoplasm progression (14; 3%, coded as AEs) were the 2 most common events leading to discontinuation in these 64 patients. Decreased platelet count was evenly distributed across disease groups. Neoplasm progression was a more common reason for discontinuation with increasing disease severity (CP-CML: 1.1%; AP-CML: 4.7%; BP-CML/Ph+ ALL: 7.4%). Most other AEs led to discontinuation for 1 patient each and included laboratory abnormalities, other disease progression terms, cardiac events, cerebrovascular events, and infections. Only 1 patient discontinued due to pancreatitis, and 1 patient due to skin conditions.

The off-treatment platelet values in the 18 patients (3.4%) who discontinued due to decreased platelet count were analysed per request by the CHMP. Some degree of recovery was seen in 13 of 18 patients after discontinuation of ponatinib (in 5 cases to normal platelet levels). The fact that two patients had decreasing values following discontinuation may be most likely explained by the underlying disease. It was also noted that several patients entering the study with low platelets (due to disease) achieved normal values during some period under therapy, indicating a treatment effect.

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

The most common serious adverse reactions >1% (treatment-emergent frequencies) were pancreatitis (5.1%), abdominal pain (3.6%), pyrexia (3.3%), anemia, (2.9%), febrile neutropenia (2.9%), platelet count decreased (2.9%), myocardial infarction (2.9%), diarrhea (1.6%), lipase increased (1.3%), neutrophil count decreased (1.3%), and pancytopenia (1.3%). Overall, the most common adverse reactions (≥20%) were platelet count decreased, rash, dry skin, and abdominal pain. The rates of treatment-related adverse events resulting in discontinuation were 10% in CP-CML, 7% in AP-CML and 3% in BP-CML/Ph+ ALL.

SAEs occurred in 284 (53.6%) patients; 171 (32.3%) were grade 3-4, and 75 (14.2%) were fatal (grade 5).

The most commonly occurring serious adverse events (in ≥2% of patients) were neoplasm progression, pneumonia, pancreatitis, febrile neutropenia, pyrexia, abdominal pain, decreased platelet count, atrial fibrillation, anaemia, and sepsis.

The SOCs with most fatal serious adverse events were Infections (15 patients; 2.8%); Nervous system disorders (7 patients- 1.3%, including 4 intracranial haemorrhage and 1 haemorrhagic cerebral infarction – i.e. bleeding events); and Cardiac disorders (8 patients; 1.5%). In the GI SOC an additional fatal bleeding event was seen – haemorrhagic gastritis. In total 6 (1.1%) fatal bleeding serious adverse events occurred.

Ponatinib is associated with severe (National Cancer Institute Common Terminology Criteria for Adverse Events grade 3 or 4) thrombocytopenia, neutropenia, and anaemia. The frequency of these events is greater in patients with accelerated phase CML (AP-CML) or blast phase CML (BP-CML)/Ph+ ALL than in chronic phase CML (CP-CML). As a consequence, patients should perform a complete blood count should be performed every 2 weeks for the first 3 months and then monthly or as clinically indicated (see SmPC sections 4.2, 4.4 and 4.8). Myelosuppression was generally reversible and usually managed by withholding Iclusig temporarily or reducing the dose. Discontinuation due to myelosuppression was infrequent (thrombocytopenia 3.6%, neutropenia and anaemia <1% each).

Ponatinib is associated with pancreatitis, the frequency of which is greater in the first 2 months of use. Serum lipase should be checked every 2 weeks for the first 2 months and then periodically thereafter. Dose interruption or reduction may be required. If lipase elevations are accompanied by abdominal symptoms, ponatinib should be withheld and patients evaluated for evidence of pancreatitis (see section 4.2 of the SmPC). Patients with a history of pancreatitis or alcohol abuse should be cautiously treated. Patients with severe or very severe hypertriglyceridemia should be appropriately managed to reduce the risk of pancreatitis.

Non-hematologic laboratory abnormalities occurred with similar incidence across disease groups except bilirubin, which was lowest in the CP-CML group (14.4% vs. 26.6% and 27.1%), increased creatinine, which was highest in the BP-CML/Ph+ ALL group (12.1% vs. 6.4% and 3.2%), and increased lipase, which was lowest in the BP-CML/Ph+ ALL group (10.3% vs. 24.3% and 26.6%). A warning has been included in section 4.4 of the SmPC.

During the initial phases of clinical development, there was insufficient safety data available to justify supratherapeutic doses in normal subjects to conduct a thorough QTc study. Instead the applicant collected ECG data from subjects enrolled into the phase 1 study, and this was continued in the phase 2 study. Overall, the incidences of QT prolongation were low in the conducted trials. However the lack of a thorough QTc study makes it difficult to completely rule out an effect of ponatinib on QT prolongation. This is acknowledged by the applicant, and appropriate wording has been included in section 4.4 of the SmPC. Further data collection is planned and ongoing in the phase 3 study with ponatinib.

Pancreatic events (24%), including pancreatitis in 7.4%, stand out as one of the major safety issues of ponatinib use, which is unlike the other TKIs with less than 1% pancreatitis. With regard to fluid retention and related AEs, ponatinib appears somewhat better than dasatinib but less favourable than nilotinib. Haematological laboratory abnormalities were similar between ponatinib and dasatinib. The GI AEs abdominal pain and constipation were more common with ponatinib compared with the two approved TKIs, but diarrhoea was more than twice as common for dasatinib, and even more frequent for bosutinib. Frequencies for any grade vomiting were very similar across TKIs, except for bosutinib that had a higher frequency. Rash occurred with similar frequencies across TKIs. Treatment-emergent grade 3/4 ALT elevations were somewhat more frequent with ponatinib use (8%) compared with dasatinib and nilotinib and similar to bosutinib. Fluid retention and oedema–group AEs occurred with an overall frequency of more than 24% with ponatinib, and peripheral oedema was reported in 14.7%, which is lower than the frequency of fluid retention with dasatinib (50%) including superficial oedema at 36%. In contrast, lower frequencies are seen for nilotinib with superficial oedema at 11% (peripheral oedema 5-6% according to Tasigna SmPC). Similarly, pleural effusion appears in falling incidence from dasatinib (22%), bosutinib (8% treatment-related), ponatinib (7.4%) and nilotinib (not reported).

A high frequency of hypophosphatemia is seen also with other TKIs. The mechanism for serum phosphorus decrease by TKIs is not well defined and several different mechanisms have been suggested

in literature, including e.g. inhibition of platelet-derived growth factor receptor (PDFGR) signalling and induction of secondary hyperparathyroidism. The clinical condition of hypophosphatemia is known to cause a number of symptoms, e.g. muscle weakness, pareses, and spasms, neurological symptoms (tiredness, cerebellar symptoms, confusion, convulsions/seizures, coma), rhabdomyolysis and haemolysis (due to reduced ability of the cells to produce ATP, leading to cellular energy depletion and resulting instability of cell membranes). Dysfunction of erythrocytes and leukocytes has also been reported, causing impaired oxygen transport and worsening of infections, respectively. The frequencies of observed events that could in theory be potential hypophosphatemia-related symptoms were investigated in relation to the observed serum phosphorous levels in pivotal Study 201. No increased frequencies of relevant events were seen in patients with hypophosphatemia compared with the overall frequencies in the study population. Only 2 of 112 patients with hypophosphatemia experienced grade 3 events, fatigues and asthenia, respectively. Thus, no immediately apparent relationship between ponatinib-induced hypophosphatemia and symptoms was revealed. Hypophosphatemia and related symptoms have been included as an important potential risk in the RMP and will be closely monitored in the phase 3 trial.

Imatinib and dasatinib have been associated with hypogammaglobulinemia, which is often implicated in recurrent or opportunistic infections (Koskela et al. 2011). Similar observations have not been made for ponatinib.

Although immunoglobulin levels were not routinely measured in clinical trials of ponatinib, most evidence indicate that infections were primarily due to decreased neutrophil count, which is a hallmark of the disease state and also a very common adverse reaction of ponatinib. The opportunistic infections observed to date were generally explained by the patients' underlying conditions.

2.6.2. Conclusions on the clinical safety

The lack of a comparative study hampers the assessment of causality of several adverse events that are also characteristic features of the diseases treated, such as the frequently occurring myelosuppression, infections, and bleeding. In line with this, lower frequencies were seen during periods of response, i.e. when symptoms of the disease are fewer. Fluid retention, GI events and hypertension are also frequent in the clinical studies of ponatinib.

While overall, the safety profile is similar to that of other TKI agents, it differs from them in the incidence of several clinically important events. Pancreatitis, uncommon with other TKIs, occurred overall in about 7.4% of ponatinib treated-patients, but rarely led to discontinuation.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

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

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 4, the PRAC considers by consensus that the risk management system for ponatinib (Iclusig) in the proposed indication in adult patients with

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

could be acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 48: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	- Pancreatitis, increased amylase and lipase - Myelosuppression - Thrombocytopenia - Neutropenia - Anemia - Infections - Skin reactions (rash, erythema, dry skin, acneiform dermatitis, exfoliative rash) - Liver function test abnormality - Edema and Fluid Retention - Cardiac failure/LV dysfunction
Important potential risks	- QT prolongation - Arrhythmias (tachycardia, atrial fibrillation) - Ischemic cardiac events - Bleeding - Hypophosphataemia and related symptoms - Pulmonary hypertension - Teratogenicity - Off-label use
Important missing information	- Treatment with ponatinib > 12 months - Treatment of patients with hepatic impairment - Treatment of patients receiving concomitant proton pump inhibitors - Treatment of patients receiving concomitantly CYP 3A4 inducers - Treatment of patients receiving concomitantly CYP 3A4 inhibitors

Summary of safety concerns	
	- Induction of cytochrome P450 isozymes - Time dependency of the pharmacokinetics of ponatinib - Use of ponatinib in the treatment of patients with newly diagnosed CML - Effect of ponatinib on male fertility - Plasma exposure to metabolites - Treatment of paediatric patients

- **Pharmacovigilance plans**

Table 49: On-going and planned studies in the PhV development plan

Study	**Protocol version**	**Protocol status**	**Planned date for submission of interim data**	**Planned date for submission of final data**
Phase 1 studies				
Evaluation of Pharmacokinetics and Safety of Ponatinib in Patients with Chronic Hepatic Impairment and Matched Healthy Subjects (Study number: AP24534-12-109)	V1	Approved	N/A	Jul 2014
An Open-Label, Nonrandomized, Inpatient/Outpatient Clinical Study to Assess the Effect of Rifampin on the Pharmacokinetics of Ponatinib, a Pan-BCR-ABL Tyrosine Kinase Inhibitor, When Administered Concomitantly in Healthy Subjects (Study number: AP24534-12-107)	V1	Approved	N/A	Dec 2013
A Clinical Study to Evaluate the Effect of Multiple Doses of Lansoprazole on the Pharmacokinetics of Ponatinib When Administered Concomitantly to Healthy Subjects (Study Number AP24534-12-108)	V1	Approved	N/A	Dec 2013
A Phase 1 Dose Escalation Trial to Determine the Safety, Tolerability and Maximum Tolerated Dose of Oral AP24534 in Patients with Refractory or Advanced Chronic Myelogenous Leukemia and other Hematologic Malignancies	V5	Approved	31 Aug 2012 (as part of the MAA)	Patients will be followed indefinitely and safety information will be reported in regular intervals (e.g. with PSURs)
Phase 2 Studies				

Study	Protocol version	Protocol status	Planned date for submission of interim data	Planned date for submission of final data
A Pivotal Phase 2 Trial of Ponatinib (AP24534) in Patients with Refractory Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia	V3	Approved	31 Aug 2012 (as part of the MAA)	Patients will be followed indefinitely and safety information will be reported in regular intervals (e.g. with PSURs)
Phase 3 studies				
A Phase 3 Randomized Open Label Study of Ponatinib versus Imatinib in Adult Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (Study Number AP24534-12-301)	V2	Approved	March 2016	Oct 2020
Clinical pharmacology				
An in vivo study of the interaction between ponatinib after repeat dosing and oral contraceptives	V1	Planned	N/A	Dec 2016
Evaluation of plasma samples longer than 24 hours after dosing in the human ADME study	V1	Planned	N/A	Dec 2013
Quantification following multiple doses in humans of new metabolites identified from the evaluation of plasma samples from the human ADME study	V1	Planned	N/A	Dec 2016
Non-clinical				
Male fertility study in rats	V1	Planned	N/A	Dec 2015
In vitro induction of CYP450 isozymes in hepatocytes	V1	Planned	N/A	Mar 2014
In vivo characterization of any additional metabolites of ponatinib	V1	Planned	N/A	Dec 2016
Modeling				
PBPK modeling of the effect of twice-daily ketoconazole on the PK of ponatinib	V1	Planned	N/A	Dec 2013
Pediatric Investigation Plan				
Quality: a study to develop an age appropriate formulation for oral use	V1	Synopsis	N/A	Dec 2018

Study	Protocol version	Protocol status	Planned date for submission of interim data	Planned date for submission of final data
Non-clinical: A toxicity study in juvenile rats	V1	Synopsis	N/A	Mar 2014
CML: An open-label multi-centre, single-agent, dose-escalation trial to investigate tolerability, safety and activity of ponatinib in children from 1 year to less than 18 years of age with malignant disease for which no effective treatment is known with an expansion cohort for children with chronic myeloid leukaemia	V1	Synopsis	N/A	Dec 2016
Ph+-ALL Randomized, multi-centre, dose-comparative, double-blind trial to investigate the safety, tolerability, activity and efficacy of ponatinib as an add-on to standard therapy in children from 1 year to less than 18 years of age with relapsed or refractory Ph+ ALL	V1	Synopsis	N/A	Dec 2019

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 50: Summary table of Risk Minimisation Measures

Safety Concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risk: Pancreatitis, increased amylase and lipase Myelosuppression Thrombocytopenia Neutropenia	Routine Pharmacovigilance Activities	Routine (SmPC) Section 4.2 (Posology and method of administration) contains advice for dose adjustments for adverse events in general, with specific instructions for myelosuppression and pancreatic events. Section 4.4 (Warnings and precautions

Safety Concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Anemia Infections Skin reactions (rash, erythema, dry skin, acneiform dermatitis, exfoliative rash) Liver function test abnormality Edema and Fluid Retention Cardiac failure/LV dysfunction		for use) contains sections on myelosuppression, pancreatitis and serum lipase, and liver function abnormality, with information and advice on managing these events. Section 4.8 (Undesirable effects) addresses the incidence of all important identified (and potential) risks, along with other common and clinically important adverse drug reactions.
Important potential risks: QT prolongation Arrhythmias (tachycardia, atrial fibrillation) Ischemic cardiac events Bleeding Hypophosphataemia and related symptoms Pulmonary hypertension Teratogenicity Off-label use	Routine Pharmacovigilance Activities Additional activity Regarding the potential risk of teratogenicity, an in vivo interaction study of the effect of ponatinib on oral contraceptives will be conducted.	Routine (SmPC) Section 4.4 (Warnings and precautions for use) contains general advice for dose modifications for all nonhaematological adverse reactions. This section also provides information on the QT evaluations that were done in the phase 1 study and the fact that a thorough QT study was not conducted. Section 4.8 (Undesirable effects) addresses the incidence of all important (identified and) potential risks, along with other common and clinically important adverse drug reactions. Section 5.1 (Pharmacodynamic properties) provides a brief summary of the results of the QT evaluation from the phase 1 study.
Important missing information: Treatment with ponatinib > 12 months Treatment of patients with hepatic impairment Treatment of patients receiving concomitant proton pump inhibitors Treatment of patients receiving	Routine Pharmacovigilance Activities Additional activities Further analysis of data received from the ongoing Phase 1 and Phase 2 study (PACE) Study in patients with hepatic impairment to evaluate the safety of	Routine (SmPC) Section 4.1 (Therapeutic indications) defines the appropriate patient population. Section 4.2 (Posology and method of administration) states that ponatinib has not been evaluated in paediatric patients and provides notice that patients with hepatic impairment may have decreased

Safety Concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
concomitantly CYP 3A4 inducers Treatment of patients receiving concomitantly CYP 3A4 inhibitors Induction of cytochrome P450 isozymes Time dependency of the pharmacokinetics of ponatinib Use of ponatinib in the treatment of patients with newly diagnosed CML Effect of ponatinib on male fertility Plasma exposure to metabolites Treatment of paediatric patients	ponatinib in this population Drug Interaction Study with ponatinib and lansoprazole Drug Interaction Study with ponatinib and rifampin PBPK modeling of the effect of twice-daily ketoconazole on the PK of ponatinib In vitro induction of CYP450 isozymes in hepatocytes Phase 3 clinical trial evaluating ponatinib vs imatinib the treatment of patients with newly diagnosed CML Nonclinical study on the effect of ponatinib on male fertility in rats Identification of metabolites in plasma longer than 24 hours after dosing. Based on the results of this analysis, any new metabolites identified will be quantified in humans after multiple dosing and in 1 nonclinical species as confirmation. Paediatric investigation plan	elimination of ponatinib. Section 4.4 (Warnings and precautions for use) cites patients with hepatic impairment as a special population for whom caution is recommended. Section 4.5 (Interaction with other medicinal products and other forms of interaction) advises that use of medicinal products that induce CYP3A or elevate gastric pH may result in reduced bioavailability of ponatinib. Section 4.6 (Fertility, pregnancy, and lactation) informs male and female patients of the lack of information on impairment of fertility. Section 5.1 (Pharmacodynamic properties) informs the median length of follow-up (10 months) and duration of treatment (up to 286 days), thereby indicating the length of time patients in the trial have been treated and evaluated. This section also informs of the lack of data in paediatric patients.

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Patients with CML and Ph+ ALL who have failed, or are intolerant to, second line tyrosine kinase inhibitor therapy with dasatinib or nilotinib, have limited therapies available, and outcomes are poor. Patients with the T315I mutation are resistant to currently available tyrosine kinase inhibitor therapy (namely imatinib, dasatinib and nilotinib). Both of the above groups have been studied in the trials submitted in support of this application.

In CP disease, achievements of cytogenetic and molecular responses are of prognostic value and consequently the most important surrogate outcome measures for a particular treatment. These outcomes are of course beneficial also in the treatment of advanced disease, but here the achievement even of a haematological response is a clinically highly relevant outcome, associated with improved symptom control. Ultimately, response to therapy may enable certain patients to proceed to allogeneic stem cell transplantation, a potentially curative intervention in CML.

The efficacy of ponatinib in the treatment of the above population of Ph+ leukaemia patients, with regards to the accepted primary endpoints, has been shown in the pivotal clinical trial submitted. With a median follow-up of 9.9 months, estimates of time related end-points especially in the population expected to have longest survival (CP-CML) were immature. However, estimates made of the duration of response, progression free survival and overall survival, point towards the responses being durable. Further analyses with additional follow-up data from an additional median of 5 months have supported the conclusions of the previous analyses. Subsequently analyses have been provided with a median follow-up of 14.5 months, and the results still support the conclusions that the responses are durable and the prospectively defined efficacy endpoints of the phase 2 study were met with statistical significance in all 6 cohorts of the study. The pivotal results were consistent with and supported by the observations in the phase 1 study.

Therefore Iclusig has shown a significant beneficial effect on the endpoints studied in the clinical trials. The effects seen are clinically relevant, and appear superior to the effects, seen in the same patient population, with the prior other TKI therapy.

Uncertainty in the knowledge about the beneficial effects.

N/A

Risks

Unfavourable effects

Many adverse events are characteristic features of the diseases treated. Thus myelosuppression was frequent and laboratory abnormalities of thrombocytopenia, anaemia, and neutropenia all occurred in > 50% of patients, with grade 3-4 AEs also very common. Infections also occurred in > 50% of patients and nearly 20% had serious infections (infection SAEs).

Pancreatitis was noted as the dose-limiting toxicity in the dose finding study. With a frequency of 7.4% in the pooled safety populations of Studies 101 and 201, it constitutes one of the major safety issues of ponatinib use.

The adverse events of myelosuppression and pancreatitis were managed effectively by the regimen of dose reduction/ dose delay used in the pivotal phase II trial. These dose recommendations have been included in section 4.2 of the SmPC.

Bleeding events occurred in 25% of all patients. Cerebral haemorrhage and gastrointestinal haemorrhage were the most commonly reported serious bleeding events, as well as the most commonly reported fatal bleeding events.

Fluid retention and oedema occurred with an overall frequency of more than 24%, and 16.3% of patients had dose reductions or drug interruptions for fluid retention events.

Gastrointestinal AEs are frequently occurring with ponatinib use, affecting 77.7% of patients; 18.7% had grade ≥3 events (almost all of these were grade 3).

Two patients discontinued due to hepatotoxicity. No cases fulfilling Hy's law were seen.

Of all 38 deaths during study that were not due to progressive disease, 5 were considered at least possibly related to study treatment. These included 2 cases of pneumonia (1 being fungal), 1 haemorrhagic gastritis, 1 myocardial infarction and 1 cardiac arrest due to diarrhoea and dehydration.

The overall pattern is that AEs of any grade and of grade ≥3 generally increase with disease severity. Multivariate analysis showed that AEs generally increased with increasing dose intensity, number of prior TKIs, time since diagnosis, and age.

Uncertainty in the knowledge about the unfavourable effects

A thorough QT/QTc study has not been conducted, and therefore an effect of ponatinib on QT prolongation cannot be definitely ruled out. Warnings and precautionary texts have been added to the product information, and further intensive ECG monitoring is planned in future studies.

The mechanism(s) for hypophosphatemia with ponatinib and other TKIs remain largely unknown and a number of different potential mechanisms have been proposed for these TKIs in the literature. The clinical relevance of decreased serum phosphorus appears to be minor based on currently available data, but should be further monitored. Hypophosphatemia and related symptoms are being included in the RMP as an important potential risk, and will be closely monitored in the phase 3 trial.

The elimination pathways of major importance have not been fully clarified. This has consequences for the interaction potential and which medicinal products interactions could be expected for on a mechanistic basis. CYP3A4 is responsible in part for the elimination, and the interaction study with ketoconazole shows an effect of 70-80 % increase in the exposure of ponatinib, that could potentially be larger.

Patients with hepatic impairment are likely at risk of higher exposure. This effect has so far not been quantified but the Applicant committed to conduct a study in patients with hepatic impairment. Exposure increase could also occur in patients with severe renal impairment, due to the presence of uremic toxins affecting also hepatically eliminated medicinal products.

Benefit-risk balance

Importance of favourable and unfavourable effects

The magnitude of response rates shown in the two clinical studies is considered very clinically relevant, especially for, but not restricted to, CML patients harbouring the T315I mutation.

The most common unfavourable effects include gastrointestinal events, rash and other skin events, infections, myelosuppression, fluid retention, pancreatitis, fatigue, and myalgia. However, most of the common unfavourable effects were well-managed with the dose reduction/ dose delay regimen used in the pivotal trial.

Benefit-risk balance

In a patient population, that includes patients with the T315I mutation, or patients who resistant to treatment with dasatinib/ nilotinib, the clinical benefits are considered relevant and outweigh the potential risks, which to large extent appear manageable. The same benefit-risk balance can also be concluded in a patient population intolerant to dasatinib or nilotinib, and for whom subsequent treatment with imatinib is clinically inappropriate. It is however noted that although patients with Ph+ ALL pre-treated with nilotinib have been included in the clinical studies, nilotinib is not approved in the treatment of Ph+ ALL patients which is reflected in section 4.1 of the SmPC.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that ponatinib is not similar to Atriance, Evoltra, Sprycel, Tasigna and Xaluprine within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Iclusig in the treatment of adult patients with

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

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 8 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted 30 days of the granting of the Marketing Authorisation.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

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

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that ponatinib is qualified as a new active substance.