Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Ponatinib

Proprietary Product Name: Iclusig

Sponsor: ARIAD Pharmaceuticals Australia Pty Ltd

April 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
AE	Adverse Event
ALL	Acute Lymphoblastic Leukaemia
ALT	Alanine Transaminase
AP-CML	Chronic myeloid leukaemia in accelerated phase
ASCT	Allogeneic Stem Cell Transplantation
AST	Aspartate Transaminase
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the curve
BP-CML	Chronic myeloid leukaemia in blast phase
CCyR	Complete Cytogenetic Response
CHR	Complete Haematological Response
C_{max}	Maximum concentration
CML	Chronic myeloid leukaemia
CP-CML	Chronic myeloid leukaemia in chronic phase
CYP	Cytochrome P450
DILI	Drug Induced Liver Injury
DLT	Dose-limiting toxicity
DoR	Duration of Response
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IV	Intravenous

Abbreviation	Meaning
MaHR	Major Haematological Response
MCyR	Major Cytogenetic Response
MTD	Maximum Tolerated Dose
OS	Overall Survival
pCRKL	Phosphorylated CRKL
PCyR	Partial Cytogenetic Response
PD	Pharmacodynamics
PFS	Progression free survival
Ph+	Philadelphia chromosome positive
PI	Product Information
PK	Pharmacokinetics
SAE	Serious Adverse Event
TGA	Therapeutic Goods Administration
TKI	Tyrosine Kinase Inhibitor
T_{max}	Time of maximum concentration

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	19 November 2014
Active ingredient:	Ponatinib
Product name:	Iclusig
Sponsor's name and address:	ARIAD Pharmaceuticals (Australia) Pty Ltd[1] 711 High St East Kew Vic 3102
Dose form:	Tablet, film coated (not scored)
Strengths:	15 mg and 45 mg
Container:	Bottle
Pack sizes:	60 tablets (15 mg) and 30 tablets (45 mg)
Approved therapeutic use:	*Iclusig is indicated for the treatment of adult patients with:* *1. Chronic phase, accelerated phase, or blast phase chronic myeloid Ieukaemia whose disease is resistant to, or who are intolerant of at least two prior tyrosine kinase inhibitors; or where there is a T315I mutation.* *2. Philadelphia chromosome-positive acute lymphoblastic Ieukaemia (Ph+ ALL) whose disease is resistant to, or who are intoIerant of dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or where there is a T315I mutation* *Therapy with Iclusig should be initiated and monitored by a haematologist with expertise in managing adult leukaemias.*
Route of administration:	Oral (PO)
Dosage:	The recommended starting dose of Iclusig is 45 mg once daily, taken at the same approximate time each day. Iclusig may be taken with or without food. For the standard dose of 45 mg once daily, a 45 mg film-coated tablet is available. Treatment should be continued as long as the patient does not show evidence of disease progression or unacceptable toxicity. Consider reducing the dose of Iclusig to 30 mg or 15 mg for chronic phase (CP) CML patients who have achieved a major cytogenetic response, especially in subjects at risk of vascular adverse events.
ARTG numbers:	212583 and 212584

[1] Agent: Specialised Therapeutics Australia Pty Ltd

Product background

This AusPAR describes the application by Specialised Therapeutics Australia Pty Ltd, on behalf of ARIAD Pharmaceuticals (Australia) Pty Ltd, to register the new chemical entity, ponatinib (Iclusig), to be used for the treatment of adult patients with chronic phase, accelerated phase or blast phase chronic myeloid leukaemia (CML) that is that is resistant or intolerant to dasatinib or nilotinib or has the T315I mutation (see below).

The proposed indications (revised by the sponsor in November 2013) were as follows:

> *Iclusig (ponatinib) is indicated for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL).*

The proposed oral dose is 45 mg once daily.

Ponatinib is what is called a *breakpoint cluster region* (BCR) – *Abelson* (ABL) tyrosine kinase inhibitor (TKI). The BCR-ABL protein produced by the t(9,22) translocation (Philadelphia chromosome [2]) has a kinase domain. The kinase function is unregulated and it causes constitutive activation of mitogenic signals, reduced apoptosis and altered adhesion properties in affected cells. Inhibition of the kinase activity by ponatinib is intended to impair the disease process. Other BCR-ABL TKIs (imatinib, dasatinib, nilotinib) have been shown to have substantial clinical activity in CML and Ph+ve ALL. A further BCR-ABL TKI, bosutinib, has been registered in Australia for the treatment of CML.

Resistance to currently available BCR-ABL TKIs can occur, most commonly through the development of mutations in the kinase domain of the BCR-ABL protein. A large number of such mutations have been described. One such mutation is the substitution of threonine at position 315 of the molecule with isoleucine (T315I). This particular mutation confers resistance by altering the binding site of the currently available TKIs to the BCR-ABL. The purported advantage of ponatinib is that it is effective in subjects who are resistant or intolerant to currently available BCR-ABL TKIs, including subjects who have the T315I mutation.

Regulatory status

Ponatinib is a new chemical entity for Australian Regulatory purposes.

Ponatinib was designated as an orphan drug by the TGA on 14 May 2013.

The current indication differs slightly in terms of defining the patient groups to be treated (which are a subset of those already identified); as this does not increase the numbers being treated, the orphan designation remains valid for the indication proposed by the sponsor and the amended indication proposed by the Delegate.

[2] The Philadelphia chromosome or Philadelphia translocation is a specific abnormality of chromosomal chromosome 22, which is unusually short, as an acquired abnormality that is most commonly associated with chronic myelogenous leukemia (CML) It is the result of a reciprocal translocation between chromosome 9 and chromosome 22, which is specifically designated t(9;22)(q34;q11). This gives rise to a fusion gene, bcr-abl, that juxtaposes the *Abl1* gene on chromosome 9 (region q34) to a part of the *BCR* ("breakpoint cluster region") gene on chromosome 22 (region q11). The presence of this translocation is a highly sensitive test for CML, since 95% of people with CML have this abnormality (the remainder have either a cryptic translocation that is invisible on G-banded chromosome preparations, or a variant translocation involving another chromosome or chromosomes as well as the long arm of chromosomes 9 and 22). However, the presence of the Philadelphia (Ph) chromosome is not sufficiently specific to diagnose CML, since it is also found in acute lymphoblastic leukemia (ALL, 25–30% in adult and 2–10% in pediatric cases) and occasionally in acute myelogenous leukemia (AML). Abl stands for "Abelson", the name of a leukemia virus which carries a similar protein.

The application letter (August 2013) sought approval of the following indication:

> *Iclusig (ponatinib) is indicated for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) that is resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy, or Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) that is resistant or intolerant to prior TKI therapy.*

At the time of the marketing suspension in the US, the TGA had received the dossier and was undertaking the first round of clinical evaluation. A stop-clock was agreed to allow submission and evaluation of the additional safety data that was presented to the European Medicines Agency (EMA), as part of the first round clinical evaluation. At this time, the sponsor proposed a revised indication. The following revised indication was proposed in November 2013:

> *Iclusig (ponatinib) is indicated for the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) that is resistant or intolerant to dasatinib or nilotinib or has the T315I mutation.*

Currently, the approvals based algorithm for CML and Ph+ ALL is complicated (Table 1): imatinib is the only agent registered as a first-line therapy for both Ph+ ALL and all phases of CML. Dasatinib is registered as first-line for CP (chronic phase) CML, and second line for all three CML phases and second-line for Ph+ ALL. Nilotinib is registered first-line for Chronic myeloid leukaemia in chronic phase (CP-CML) and second-line for CP and Accelerated Phase (AP)-CML but for neither BP (blast phase) CML nor Ph+ ALL. Bosutinib was approved in Australia in May 2014 for CP, AP and BP-CML but not Ph+ ALL after the failure of at least 2 prior therapies.

Thus, in the Australian context, the sponsor is seeking approval for use potentially second line after dasatinib or nilotinib for CP-CML, third line for AP-CML (assuming imatinib first then dasatinib or nilotinib) or third line for BP-CML after imatinib or dasatinib. The recent approval of bosutinib for the third line treatment of all phases of CML occurred after the sponsor's submission and needs to be factored in for the treatment of patients with CML and the indication for ponatinib.

Table 1. Approved and proposed indications for BCR-ABL TKIs in Australia

	Imatinib	**Dasatinib**	**Nilotinib**	**Bosutinib**	**Ponatinib** [1] (proposed)
CML indications					
CML – First line treatment	CP, AP, BP	CP only	CP only	-	-
CML – after failure of imatinib	-	CP, AP, BP	CP, AP only	-	-
CML – after failure of dasatinib/nilotinib	- [2]	-	-	CP, AP, BP[3]	CP, AP, BP
Ph+ve ALL indications					
Ph+ve ALL – First line	In combination with chemotherapy	-	-	-	-
Ph+ve ALL – 2nd line	Relapsed/refractory disease	After failure of 'prior therapy'	-	-	After failure/intolerance of dasatinib or nilotinib

(1) Ponatinib is also proposed for use in subjects with the T315I mutation, regardless of stage of disease.
(2) The approved indication for imatinib is for 'the treatment of patients with CML'. However, evidence to support the efficacy and safety of imatinib after failure of dasatinib has not been submitted.
3) Approved after >2 TKIs; AP=accelerated phase; BP=blast phase; CP=chronic phase

Accelerated approval of ponatinib in the United States was granted in December 2012 (Table 2). However, the FDA subsequently raised concerns regarding a high incidence of vascular adverse events observed with longer-term follow-up of subjects in the submitted clinical trials. The Phase III trial comparing the use of ponatinib versus imatinib in newly diagnosed CP-CML was terminated. As a result of the vascular adverse event findings, the marketing approval was temporarily suspended in October 2013. Following changes to the prescribing information (including a revised indication) and the introduction of a risk evaluation and mitigation strategy (REMS), the FDA announced in December 2013 that the marketing suspension would be lifted.

Marketing authorisation of ponatinib in Europe was approved by the EMA in July 2013 (Table 2). Following the FDA's actions in October 2013, the EMA conducted a preliminary review of additional safety data and made some amendments to the prescribing information. It announced in December 2013 that it would be undertaking a further in-depth review of the drug, with an expected completion date of May 2014. This was not available at the time of this report.

Swissmedic approval for the following indications was granted on 12 February, 2014:

> *Iclusig is indicated in adult patients suffering from:*
>
> - *T315I-positive Philadelphia-positive (Ph+) chronic myeloid leukemia (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ acute lymphoblastic leukemia, or*
> - *Ph+ chronic myeloid leukaemia (chronic phase, accelerated phase or blast phase) or Ph+ acute lymphoblastic leukaemia for whom a treatment with other bcr-abl tyrosine kinase inhibitors is not appropriate.*

At the time of lodgement in Australia (August 2013), applications for marketing approval had also been lodged in Canada (May 2013) with a decision yet to be made.

Table 2. International regulatory status

Country	Approval Date	Launch Date	Trade Name	Strength	Indication
United States (NDA 203469) **Filed by:** ARIAD Pharmaceuticals, Inc.	Initial approval: 14 December 2012 (priority review) (Filed 30 July 2012) Revised indication: 20 December 2013 (labeling supplement)	Initial Launch: 04 January 2013 Re-launch Date: 17 January 2014	ICLUSIG	15 and 45 mg	Iclusig (ponatinib) is a kinase inhibitor indicated for the: •Treatment of adult patients with T315I-positive chronic myeloid leukemia (CML) (chronic phase, accelerated phase, or blast phase) and T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL). •Treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.
Europe (European Medicines Agency) (H0002695) **Filed by:** ARIAD Pharma Ltd.	01 July 2013 (Filed 31 August 2012)	24 July 2013	ICLUSIG	15 and 45 mg	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.
Switzerland (Swissmedic) Filed by: ARIAD Pharmaceuticals (Europe) Sarl	12 February 2014 (fast track review) (Filed 26 April 2013)	26 February 2014	ICLUSIG	15 and 45 mg	Iclusig is indicated in adult patients suffering from: •T315I-positive Philadephia-positive (Ph+) chronic myeloid leukemia (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ acute lymphoblastic leukemia, or •Ph+ chronic myeloid leukemia (chronic phase, accelerated phase or blast phase) or Ph+ acute lymphoblastic leukemia for whom a treatment with other c-abl tyrosine kinase inhibitors is not appropriate.
Canada (Health Canada) (NDS Control # 165121) **Filed by:** ARIAD Pharmaceuticals, Inc.	pending (Filed 22 May 2013)	pending	ICLUSIG	15 and 45 mg	ICLUSIG is indicated for: •the treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) resistant or intolerant to dasatinib or nilotinib or for whom other tyrosine kinase inhibitors (TKI) are not appropriate •the treatment of adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) resistant or intolerant to dasatinib or nilotinib or for whom other TKIs are not appropriate.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

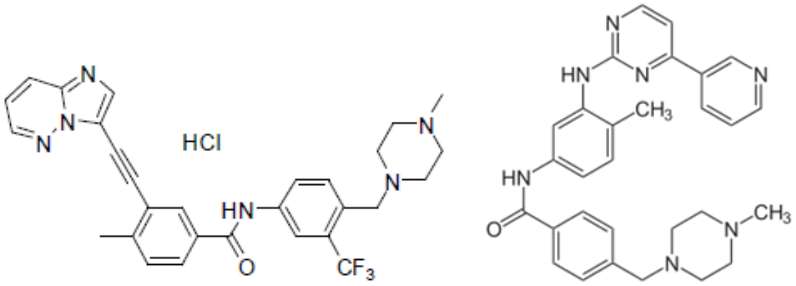
II. Quality findings

Drug substance (active ingredient)

Ponatinib is a substituted imidazo[1,2-b]pyridazin: the structure is shown below (Figure 1). Ponatinib is not chiral. It does contain an alkyne (acetylene) group, which is relatively rare in drug substances (compared to terbinafine, oxybutynin and norethisterone) but which does not confer unusual reactivity (except when unusually conjugated like calicheamicin).

Structurally there is some analogy to imatinib (Glivec 50, 100, 400 mg tablets or capsules [Novartis Pharmaceuticals Australia Pty Ltd]) (Figure 1).

Figure 1: Structure of ponatinib (HCl) and imatinib



ponatinib hydrochloride **imatinib**

Ponatinib is made by chemical synthesis. The drug substance is anhydrous ponatinib hydrochloride, which is crystalline. Only one polymorphic form was used.

Ponatinib is basic and solubility is markedly higher in acid than at neutral pH.

The drug substance is not micronised; it consists of a mixture of smaller particles (1 to 30 µm) and aggregates of these (15 to 300 µm). These agglomerates are apparently broken up during tablet manufacture. Drug particle size differences did not correlate with in vitro tablet dissolution.

As a new drug, there are no official monographs. Impurity levels are low. The drug is stable on storage.

Drug product

ARIAD seeks to register 15 mg and 5 mg film-coated, immediate release ponatinib tablets. Both strengths are white, biconvex, round tablets (approximately 6.35 mm and 9.5 mm diameter). They are differentiated by size and by tablet debossing on one side ('A5' for 15 mg; 'AP4' for 45 mg). The tablets are not scored.

The proposed packs are plastic bottles of 60 (15 mg) or 30 (45 mg).[3] The bottles have child resistant lids.

Tablets are formulated with ponatinib hydrochloride but labelled with the corresponding ponatinib content, in keeping with current practice. Excipients are conventional; the two strengths are direct scales. The tablets are made by direct compression.

Clinical trial formulations

Only four dosage forms have been administered in clinical studies:

Drug-in-capsule (2 mg)	Study 101 Dose-Escalation
Formulated capsules (5 and 15 mg)	Study 101 Dose-Escalation
[^{14}C][4]-ponatinib-in-capsule (15mg)	Study 104 ADME[5]
Film-coated tablets (15 and 45 mg)	Study 101 and all other studies

[3] Initially packs of 180 tablets (15 mg) and 90 tablets (45 mg) were also proposed.
[4] Radioactively (carbon) labelled
[5] Absorption, Distribution, Metabolism, Excretion (ADME)

The initial dose-escalation study (101) used capsule formulations and 15 mg tablets. The 15 mg and 45 mg tablets were developed with a similar formulation to the dry blended capsule formulation but an increased drug load. Tablets of both strengths were used in the pivotal efficacy study (AP24534-10-201).

Dissolution profiles of the 15 mg and 45 mg tablets are similar.

Impurity levels are fairly low; the most significant related substances are metabolites but levels in tablets are low.

There are some stability issues with the tablets and the proposed shelf life is not supported. Tablet dissolution declines on storage. The shelf life is likely to be better with bottle packs containing a desiccant and this is currently being investigated by ARIAD.[6] A shelf life has not yet been confirmed. Revised container, pack size and storage condition details should be available at the time of the meeting of the TGA's Advisory Committee on Prescription Medicines (ACPM).

Biopharmaceutics

Ponatinib hydrochloride is in Biopharmaceutics Classification System ('BCS') Class 2 (low solubility – high permeability). As noted above, because ponatinib only readily dissolves in acid, there is a *potential* for incomplete absorption in patients with achlorhydria, and a potential interaction with proton pump inhibitors, histamine 2 (H2) antagonists and antacids.[7]

Ponatinib is extensively metabolised, especially by cytochrome P450 isozyme CYP3A4. Radiolabelled ponatinib is mainly eliminated via faeces. The major metabolite is AP24600, formed by amide hydrolysis. Metabolites are not pharmacologically active. Pharmacokinetics are reported to be approximately linear.

No human absolute bioavailability study has been undertaken. Such studies are normally expected as part of the underlying pharmacokinetic characterisation of new chemical entities. ARIAD notes that oral solution doses (15 mg/kg) given to rats gave an absolute oral ponatinib bioavailability of 54%. Oral capsule doses of 2 to 3 mg/kg given to monkeys gave an absolute oral bioavailability of 20.6%.

The sponsor notes ADME Study 104 in which 45 mg (three 15 mg capsules containing [^{14}C]-ponatinib) was given to six healthy subjects. The majority of radioactivity was recovered in faeces (approximately 87% of dose, with approximately 5% in urine), chiefly as metabolites. This is consistent with extensive absorption, as long as the metabolism cannot occur in the gut.

The sponsor argues that reproducible systemic exposures were seen in the pharmacokinetic studies and states that since they have no plans to explore other dosage forms, considers that the undertaking of an absolute bioavailability study is not critical.

[6] Data was subsequently submitted by the sponsor to support the shelf life.

[7] The following is an excerpt from the approved PI for Iclusig: Elevated gastric pH: The aqueous solubility of ponatinib is pH dependent, with higher pH resulting in lower solubility. Administration of a single 45 mg dose of ponatinib following multiple doses of a potent inhibitor of gastric acid secretion (lansoprazole 60 mg QD for 2 days) resulted in a minor reductions in ponatinib C_{max} (25%) without a change in overall systemic exposure ($AUC_{0\text{-}inf}$), respective to those seen when ponatinib was administered alone. Median T_{max} was increased by 1 hour when ponatinib was administered following lansoprazole pretreatment. ICLUSIG may be administered concurrently with drugs that raise gastric pH without the need for adjustment of ICLUSIG dose or separation of administration.

Absorption

Absorption of ponatinib from the tablets is relatively slow (time to peak plasma concentration (T_{max}) 4 to 6 h). Profiles are otherwise conventional and intra subject variability is low.

In Study 102, twenty four healthy subjects were each given tablet doses with one of three food treatments in a crossover design. One subject had unmeasurable ponatinib concentrations after the third dose (a high fat meal: food is expected to stimulate acid secretion, which would be predicted to increase dissolution and bioavailability). It is conceivable that this is due to failure of the particular tablet to release ponatinib over 96 hours. But ARIAD hypothesises that, despite visual mouth and hand checks performed by the site staff, this subject did not taken this tablet dose.

Bioavailability

The initial dose-escalation study (101) used capsule formulations and 15 mg tablets. ARIAD has estimated the steady state bioavailability of these dose forms in a subset of patients given 45 and 60 mg doses and analysable after 28 days dosing. ARIAD concludes that 'there was no evidence of statistically important differences between the tablet and capsule formulations' (rather than the stricter test of formal bioequivalence).

Food effect

Study AP24534-11-102 was a single-dose, randomised, open-label, 3-period, 6-sequence crossover, study in twenty four healthy subjects. Single oral 45 mg tablet doses were given after an overnight fast, immediately after a high-fat meal, and after a low-fat meal, all with 240 mL water. Plasma levels of ponatinib were measured. Food did not markedly affect T_{max} or peak plasma concentration (C_{max}); a high fat meal slightly increased absorption (area under the plasma concentration versus time curve (AUC)) but with all treatments bioequivalence within standard limits. Thus, food does not affect absorption.

Advisory committee considerations

In keeping with recent practice, this application has not been referred to the Pharmaceutical Subcommittee (PSC) of ACPM because the quality and biopharmaceutic data did not raise unusual issues.

Quality summary and conclusions

There are stability issues with the tablets and a shelf life cannot yet be recommended. Stability is likely to be better with bottle packs containing a desiccant which are currently being investigated by ARIAD.[8] Updated details should be available at the time of the ACPM meeting.

Registration is otherwise recommended with respect to quality and biopharmaceutic aspects.

III. Nonclinical findings

Introduction

The submitted nonclinical data were in accordance with the relevant The International Conference on Harmonisation of Technical Requirements for Registration of

[8] Data was subsequently submitted which supported the 18 month shelf life when stored below 30ºC.

Pharmaceuticals for Human Use (ICH) guideline for the nonclinical assessment of anticancer pharmaceuticals.[9] The overall quality of the dossier was high with all pivotal safety studies conducted under Good Laboratory Practice (GLP) conditions.

Pharmacology

Primary pharmacology

Rationale and mechanism of action

Rearrangement of the Philadelphia chromosome can lead to the generation of a gene encoding the fusion protein, BCR-ABL, a constitutively active tyrosine kinase that gives rise to CML and a subset of ALL (Ph+ ALL). Mutations in the ABL kinase domain confer resistance to existing BCR-ABL targeting agents, imatinib, nilotinib and dasatinib. While the second generation BCR-ABL inhibitors, nilotinib and dasatinib, are active against some imatinib-resistant BCR-ABL mutants, they are inactive against a subset of BCR-ABL mutants.[10] Ponatinib was developed to be active against native BCR-ABL and its mutants that are resistant to the existing agents; imatinib, nilotinib and dasatinib.

In vitro

In vitro, ponatinib inhibited wild-type ABL and 5 ABL mutants[11] (50% inhibitory concentration (IC_{50}) 0.3 to 2 nM) and inhibited the viability of human leukaemia cells and BaF3 cells expressing BCR-ABL or one of its mutants[12] (IC_{50} 0.3–36 nM). Ponatinib had the least activity against E255K, E255V and T315I (IC_{50} values of 14, 36 and 11, respectively). No inhibitory activity was seen against BCR-ABL negative cells (IC_{50} >1 μM; approximately10 times the clinical C_{max}), confirming the effect on viability was due to inhibition of the BCR-ABL tyrosine kinase activity. Ponatinib inhibited the viability of BaF3 cells (murine pro-B cell line) expressing mutants resistant (or relatively resistant) to imatinib, nilotinib and dasatinib[13], imatinib and nilotinib[14] or imatinib only[15]. In cells, ponatinib inhibited the phosphorylation of BCR-ABL and BCR-ABL T315I (IC_{50} 7 to 25 nM and 78 nM, respectively) and their downstream target, CrkL (IC_{50} 68 to 83 nM and 580 nM, respectively), suggesting an inhibition of signalling from BCR-ABL and the T315I mutant. Neither dasatinib nor nilotinib inhibited signalling from BCR-ABL T315I. The IC_{50} values for ponatinib against BCR-ABL and its mutants are within clinically relevant plasma concentrations (C_{max} 103 nM; C_{trough} 64 nM). Overall, the in vitro data support the proposed clinical use of ponatinib in BCR-ABL positive leukaemia indications and in patients with imatinib, nilotinib and dasatinib resistant BCR-ABL mutations[16].

The main human metabolite, AP24600, had no inhibitory activity against wild-type ABL and the T315I mutant (IC_{50} >3 μM; 28 times the clinical C_{max}) and no cytotoxic activity on BaF3 expressing these proteins (IC_{50} >10 μM; 92 times the clinical C_{max}). Therefore, AP24600 is not expected to contribute to the efficacy of ponatinib during clinical use.

The N-desmethyl metabolite had 4 fold less inhibitory activity on wild-type ABL and the T315I mutant (Huang *et al.*, 2010). Given that this is only a minor metabolite (exposures 2

[9] EMEA/CHMP/ICH/646107/2008 ICH Topic S9 Note for guidance on nonclinical evaluation for anticancer pharmaceuticals. ICH9 Topic S9
[10] V299L, T315A, F317L/V/I/C, Y253H, E255 K/V or F359V/C/I
[11] Q252H, Y253F, T315I, M351T and H396P
[12] M244V, G250E, Q252H, Y253F/H, E255K/V, T315A/I, F317L/V, M351T, F359V and H396P
[13] T315A/I
[14] Y253H, E255K/V and F359V
[15] M244V, G250E, Q252H, F317L/V and M351T
[16] M244V, G250E, Q252H, Y253F/H, E255K/V, T315A/I, F317L/V, M351T, F359V and H396P

to 4% of the parent), this metabolite is unlikely to significantly contribute to the efficacy of the drug.

In vivo

The anti-tumour efficacy of ponatinib was assessed in mice bearing allografts and xenografts of cells expressing native BCR-ABL or the T315I mutant. In mouse CML models (IV injection of cells expressing native BCR-ABL or its mutant, T315I), a dose-dependent increase in survival was observed; a 50 to 86% increase at 5 to 10 mg/kg/day PO in animals with native BCR-ABL leukaemia and, at higher doses (15 to 25 mg/kg/day PO), a 63 to 88% increase in animals with the T315I mutant. Most of the deaths (90%) occurred after the cessation of treatment. No tumour regression was observed in either model. Tumour regression was observed in mice bearing subcutaneous (SC) xenografts[17] of human CML cells expressing native BCR-ABL (at ≥2.5 mg/kg/day PO) and mice bearing SC allografts[18] of the T315I mutant (at 50 mg/kg/day PO). Tumour stasis was seen in the latter model at 30 mg/kg/day PO. Overall, the in vivo data support the use of ponatinib for the treatment of patients with CML.

In mouse CML models, doses resulting in significant prolongation of survival (15 to 45 mg/m2) are similar to the proposed clinical dose (30 mg/m2), thus supporting the proposed clinical dose. In Pharmacokinetic (PK)/Pharmacodynamic (PD) models (mice with SC xenografts), a sustained (24 h) decrease in BCR-ABL phosphorylation was observed at 5 mg/kg (Exposure ratio human: animal using AUC (ERAUC) 0.7), while a sustained decrease in BCR-ABL (T315I) was observed at higher doses (30 mg/kg; ERAUC 3.7). Ponatinib was clearly less efficacious in models expressing the T315I mutant than those expressing the native BCR-ABL. Given that the in vitro data indicated ponatinib had less activity at E255K/V mutants than T315I, ponatinib may be less efficacious in patients carrying these mutations.

Resistance

Cells expressing native BCR-ABL were subjected to chemical mutagenesis and challenged with different concentrations of ponatinib in an attempt to identify ponatinib-resistant mutants. BCR-ABL mutants surviving 20 nM ponatinib were T315I and E255V. There were no mutants that were resistant to 40 nM ponatinib, suggesting the possibility of a single mutation conferring resistance to ponatinib at trough plasma concentrations ($C_{trough)}$ is low, though as stated above, less efficacy may be seen in patients carrying E255K/V mutations. The ability of compound mutations conferring resistance to ponatinib has not been assessed and therefore cannot be dismissed.

Secondary pharmacodynamics and safety pharmacology

Ponatinib was assessed for inhibitory activity at 221 additional kinases and their mutants. Significant inhibitory activity was seen at the *rearranged during transfection* (RET) gene, FMS[19]-like tyrosine kinase (FLT3), stem cell factor receptor (KIT) and members of the fibroblast growth factor receptors (FGFR), Platelet-derived growth factor receptors (PDGFR), Vascular Endothelial Growth Factor Receptors (VEGFR), ephrin (EPH) family of receptors and Proto-oncogene tyrosine-protein kinase (SRC) families of kinases. The IC_{50} values (≤20 nM) are within the clinical plasma concentration range of ponatinib. Interactions at other enzymes, receptors or ion channels were not assessed.

Specialised safety pharmacology studies assessed effects on the cardiovascular, respiratory, renal, gastrointestinal and central nervous systems (CNS). All studies were GLP compliant. CNS function in mice (at ≤100 mg/kg PO) and respiratory function in rats

[17] Xenograft: a graft obtained from a member of one species and transplanted to a member of another
[18] Allograft: a tissue graft from a donor of the same species as the recipient but not genetically identical
[19] FMS is a proto-oncogene that encodes the tyrosine kinase transmembrane receptor for colony stimulating factor 1 receptor (CSF1R).

(at ≤30 mg/kg PO) were unaffected by treatment. Estimated C_{max} values were 3907 ng/mL in mice (from single-dose study ARP073) and 957 ng/mL in rats (from single-dose study QAA00120), which is 71 and 17 times the clinical C_{max}, respectively. Blood pressure and heart rate were also unaffected in monkeys at ≤6 mg/kg/day PO (C_{max} 632 ng/mL [14 day study]). While a concentration-dependent inhibition of hERG K+ channel tail current was seen with ponatinib, the IC_{50} value (2.33 μM) is approximately 11000 times higher than the clinical free plasma C_{max}, and therefore ponatinib is not predicted to prolong the QT[20] interval in patients. Systolic heart murmurs were seen in some monkeys that received ≥1 mg/kg/day PO ponatinib (exposure ratio based on C_{max} [ER_{Cmax}] 0.3) (see *Repeat-dose toxicity* below) but no abnormalities were seen in electrocardiograms from Cynomolgus monkeys that received ≤5 mg/kg/day PO (C_{max} 662 ng/mL [28 day study]; ER_{Cmax} 12).

A decrease in gastric emptying and a diuretic effect were seen in rats that received ≥3 mg/kg PO ponatinib (estimated C_{max} 40 ng/mL [from the 14 day study ARP038]). These effects are likely to be clinically relevant. Overall, adverse effects on the cardiovascular, respiratory and central nervous systems are not predicted during clinical use. Decreased gastric emptying and diuresis may occur in patients taking ponatinib. Heart murmurs in monkeys , with an unknown underlying cause at subclinical exposures, suggest some adverse cardiovascular findings may be seen during clinical use.

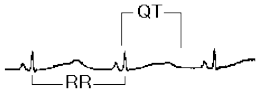
Pharmacokinetics

Following oral dosing, peak plasma levels of ponatinib were generally seen 2 to 8 h postdose in mice, dogs, Cynomolgus monkeys and human subjects. Oral bioavailability was moderate in rats (54%) and low in Cynomolgus monkeys (14%). Absolute bioavailability has not been assessed in human subjects. Exposures were generally dose-proportional in mice and rats and greater than dose-proportional in Cynomolgus monkeys. There were no obvious sex differences in the plasma kinetics of ponatinib in mice, rats or monkeys. The apparent plasma elimination half-life in these species appeared to increase with dose (PO only) (half-life ($t_{½}$) 3 to 39 h).

In clinical studies, the $t_{½}$ was 25 h at the maximum dose of 45 mg. The acid hydrolysis product (AP24600) was a major metabolite in human plasma with exposures (AUC) 41% of the parent (on a molar basis). Exposures to AP24600 were high following oral dosing to mice and rats (290% and 120% of the ponatinib exposures[21]). This metabolite was only present at trace levels in monkey plasma. In rats, AP24600 exposures were much lower with IV dosing (metabolite to ponatinib AUC approximately 50%), suggesting some pre-systemic metabolism. Exposures in male rats (less so in females) increased with repeat-dosing, suggesting drug accumulation. Exposures in monkeys were higher on Day 14/15 than Day 1, after which steady state was reached.

Plasma protein binding by ponatinib was high and independent of concentration in the plasma of mice, rats, monkeys and humans (99.8 to 99.9%). Plasma protein binding by AP24600 was similar in rat and human plasma (94 to 95%). There was no specific distribution of ponatinib into red blood cells. Following IV dosing, the volume of distribution was greater than total body water in rats and monkeys, suggesting extensive extravascular distribution. Consistent with this, tissue distribution in pigmented rats was

[20] In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle (see figure below). The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death.



[21] Molar basis using data from repeat-dose toxicity studies.

rapid and wide following oral dosing with ^{14}C-ponatinib. Aside from organs involved in excretion, high levels of radioactivity were seen in the brain, uveal tract, adrenal, thyroid, pituitary and Harderian glands, heart muscle, lung and spleen. Some of these organs were target organs for toxicity with ponatinib. The specific binding and retention of radioactivity to the uveal tract of pigmented (but not albino) rats (with a $t_{½}$ 24 times higher than the plasma $t_{½}$) may indicate melanin binding.

Ponatinib was extensively metabolised in rats and humans (representing only 19 to 26% of the circulating drug-related material) and moderately metabolised in mice and monkeys (38 to 56% of the circulating drug-related material). At least 33 metabolites were identified across species. Metabolism of ponatinib involved hydrolysis of the amide linkage (to AP24600 and an aniline product), oxidative dealkylation to remove the piperazine ring, N-demethylation, hydroxylation, N-oxidation, glucuronidation, sulfation or glucuronidation of oxidative metabolites and glucuronidation of the acid hydrolysis product. Three minor circulating metabolites in human plasma (≤7% of total drug-related material) were not detected in the plasma of rats or Cynomolgus monkeys, the species used in the toxicity studies. However, two of these were detected in the excreta of rats and monkeys and all three were detected in the plasma of mice, the third species used in the toxicity studies (albeit a non-pivotal one). AP24600, the acid hydrolysis product (which could be formed from ponatinib or some of its oxidative metabolites), was a significant circulating metabolite in mice, rats and humans but only present at trace levels in monkeys. Enzymes involved in the hydrolytic reaction were not identified. AP24600 was not detectable in liver or intestinal microsome or hepatocyte incubations. This reaction is likely to be mediated by amidases (potentially multiple), with some metabolism possibly occurring in the gut. In vitro studies indicated an involvement of cytochrome P450 isozymes CYP3A4 and 2C8 and to a lesser degree CYP2D6 in the formation of the oxidative metabolites, N-desmethyl ponatinib and ponatinib N-oxide.

Excretion of ponatinib and/or its metabolites was predominantly in the faeces in rats, monkeys and human subjects (>70%). Ponatinib was the main drug-related species in the faeces of rats and monkeys and was a significant component in human faeces. Drug-related material in urine was predominantly metabolites (AP24600 and glucuronides). Significant biliary excretion was seen in rats (54%).

Overall, the pharmacokinetic profile of ponatinib was qualitatively similar in mice, rats, Cynomolgus monkeys and humans to support the choice of animal species for toxicity studies. While the metabolite, AP24600, is only produced in low levels in Cynomolgus monkeys, the rat studies should be sufficient to assess the safety of this metabolite.

Pharmacokinetic drug interactions

Ponatinib undergoes extensive metabolism. Formation of the main metabolite, AP24600, involves hydrolysis of the amide linkage. Enzymes involved in this reaction have not been identified but as this reaction is likely to be mediated by multiple enzymes, co-administered drugs are not expected significantly affect this reaction. Other metabolic reactions of ponatinib involve CYP3A4, 2C8 and to a lesser extent CYP2D6. Therefore, inhibitors/inducers of these enzymes may alter the exposure to ponatinib. It is stated in the Product Information document that co-administration with the CYP3A4 inhibitor ketoconazole increased the systemic exposure to ponatinib in human subjects (the AUC increased by 78%). While some inhibitory activity was seen on CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5, the IC_{50} values (5.2–13.6 μM) are approximately 25000 times the clinical free C_{max} of ponatinib and therefore this activity is not expected to be clinically-relevant. The main human metabolite, AP24600, had no inhibitory activity on these enzymes. In human hepatocytes, ponatinib did not induce the expression of CYP2B6. While some induction of CYP3A4 activity and messenger ribonucleic acid (mRNA) levels was observed, the maximum induction was low (<2 times) and there was no clear concentration relationship, and the induction is unlikely to be clinically meaningful.

Ponatinib induced the expression of CYP1A2 (mRNA and activity) in human hepatocytes, but minimal induction was observed at clinically relevant concentrations (0.05 to 0.2 μM [total]). Overall, ponatinib is not expected to alter the exposure of drugs that are CYP450 substrates.

Ponatinib was not a substrate of P-glycoprotein, Breast Cancer Resistance Protein (BCRP), Organic Anion Transporting Polypeptide subtypes 1B1 and 1B3 (OATP1B1 and OATP1B3) or organic cation transporters 1 (OCT1), therefore inhibitors/inducers of these transporters are not expected to alter the disposition of ponatinib. No significant inhibition of OATP1B1, OATP1B3, OCT1, OCT2, OAT1 or OAT3 transport was observed with 2 μM ponatinib (9500 times the clinical free plasma C_{max}). Therefore, ponatinib is not expected to alter the disposition of co-administered drugs that are substrates of these transporters. Ponatinib did not induce P-glycoprotein expression but was shown to be an inhibitor of P-glycoprotein activity (IC_{50} 0.491 μM), BCRP activity (IC_{50} 0.013 μM) and Bile Salt Export Pump (BSEP) activity (IC_{50} 32 μM). As the intestinal concentrations of ponatinib are estimated to be significantly higher than the IC_{50} values of P-glycoprotein and BCRP (338 μM), ponatinib has the potential to increase the systemic exposures of co-administered drugs that are substrates of P-glycoprotein or BCRP.

In summary, CYP3A4 inhibitors/inducers and possibly CYP2C8 inhibitors, could alter the systemic exposure to ponatinib. Ponatinib is not expected to alter the exposure of co-administered drugs that are CYP450 substrates. Ponatinib may increase the exposure of co-administered drugs that are substrates of P-glycoprotein or BCRP.

Toxicology

Acute toxicity

Single-dose toxicity studies by the oral route were conducted in mice, rats and Cynomolgus monkeys. The pivotal studies were GLP compliant and were generally adequately conducted according to the relevant European Union (EU) guideline (3BS1a).[22] The maximum non-lethal dose was 500 mg/kg PO in mice, <10 mg/kg PO in rats and the highest tested dose, 45 mg/kg PO, in monkeys. Exposures at these doses were (at least) 50, <6 and 40 times the clinical AUC in mice, rats and monkeys, respectively, suggesting a moderate to high order of toxicity. Clinical signs were generally similar across species; rough hair coat or ruffled fur, and red material around nose and paws (rodents), skin erythema (all species), decreased activity (at high oral doses) and signs of immunosuppression (rats and monkeys). Target organs for toxicity, depending on dose, included the thyroid and pituitary glands, intestine, pancreas, spleen and skin. Fluid was seen in the thoracic cavity of rodents that received high oral doses of ponatinib (≥125 mg/kg PO). Significant increases in liver enzymes in rats, suggest the liver may also be a target organ.

Repeat-dose toxicity

Repeat-dose toxicity studies by the oral route were conducted in mice (2 weeks), rats (up to 6 months) and Cynomolgus monkeys (up to 6 months). There was limited reporting in the mouse study, thus the discussion below will focus primarily on findings in rats and monkeys. Rats are considered an appropriate species based on pharmacokinetic parameters. While monkeys do not produce significant amounts of the main human metabolite, AP24600, sufficient exposures to this metabolite are likely to have been achieved in the rat studies to adequately assess its toxicity. Cynomolgus monkeys have been used previously to assess the toxicity of other BCR-ABL inhibitors (nilotinib,

[22] 3BS1 Note for guidance on single dose toxicity.

dasatinib and imatinib) and may be considered an acceptable choice as the non-rodent species. The duration of the pivotal studies (6 months), group sizes and the use of both sexes were consistent with relevant guidelines. Dosing in the pivotal rat study was limited by toxicity (and deaths). The maximum dose in the 6 month monkey study (2 mg/kg/day PO) did not result in overt signs of toxicity, aside from diarrhoea; there were no effects on body weight or body weight gain. Higher doses may have been achievable but deaths and effects on body weight were seen in the 28 day study at the only slightly higher dose of 5 mg/kg/day PO. Therefore, based on the toxicities observed in the 28 day study, the maximum dose chosen in the pivotal study seems reasonable. Unfortunately, it appears equivalent doses resulted in lower exposures in the 6 month study, compromising its utility.

Relative exposure

Maximum exposures (AUC) achieved in the pivotal studies were low, being similar to or below the clinical AUC (Table 3). Similarly low margins were reported in pivotal studies with nilotinib and dasatinib. Higher exposures would not have been possible in rats due to toxicity but higher exposures (up to 12 times the clinical AUC) were observed in the shorter term monkey studies. As generally subclinical exposures were achieved in the toxicity studies, the majority of the findings described below should be assumed to be potentially clinically relevant.

Table 3. Relative exposure in selected repeat-dose toxicity studies

Species						
					AUC	C_{max}
Rat (SD)	28 days *[Study QAA00122]*	1.5	1.36	54.2	1.1	1.0
		3	0.82	82.8	0.7	1.5
	6 months *[Study QAA00193]*	0.25	0.058	4.97	0.05	0.09
		0.75	0.41	25.5	0.3	0.5
		2	1.25	73.3	1.0	1.3
Monkey (Cynomolgus)	14 days *[Study QAA00113]*	2	1.21	137	1.0	2.5
		6	14.3	632	12	12
	28 days *[Study QAA00121]*	1	0.14	17.9	0.1	0.3
		2.5	1.46	130	1.2	2.4
		5	6.85	467	6	8.5
	6 months *[Study QAA00194]*	0.25	0.018	3.02	0.02	0.06
		0.75	0.11	16.5	0.09	0.3
		2	0.61	72.4	0.5	1.3
Human	–	[45mg	1.20	54.7	–	–

Species	Study duration	Dose mg/k g/day]	$AUC_{0-24\,h}$ µg·h/mL)	C_{max} ng/mL	Exposure ratio based on	

Data from the last sampling day; average of both sexes

Major toxicities

In general, the toxicity profile of ponatinib was similar to others in the pharmacological class (such as dasatinib and imatinib), with the liver, heart, lymphoid organs, and male and female reproductive organs as target organs for toxicity with effects on the coagulation system and red blood cell parameters observed. Additional organs for toxicity included the thyroid and adrenal glands, bones, pancreas, skin and kidneys.

Reversible elevations in liver enzymes, alanine aminotransferase (ALT) (1.9 to 4.5 times) and aspartate aminotransferase (AST) (3 to 10 times) were observed in monkeys that received ≥0.75 mg/kg/day PO ponatinib for 6 months (exposure ratio based on AUC [ERAUC] 0.09). There was not always a histopathological correlate, though hepatocellular necrosis was observed in some animals. Large increases in ALT and AST levels (1.5 to 4 times) were observed in rats that received a single high oral dose of ponatinib (≥30 mg/kg PO) but without evidence of liver damage. Nonetheless, given the magnitude of the increase in ALT, even in the absence of histological changes, the elevated liver enzymes indicate the potential for hepatic injury during clinical use.[23]

Lymphoid depletion of the thymus, spleen, lymph nodes and/or gut associated lymphoid tissue was seen in both rats (2 mg/kg/day PO for 6 months) and monkeys (≥2 mg/kg/day PO for at least 28 days). Decreases in circulating lymphocytes were not always consistent or as dramatic as one might expect based on the changes in the lymphoid organs; lymphoid depletion was often evident in the absence of a significant reduction in circulating lymphocytes. The lymphoid depletion had not fully reversed after a 4 week treatment free period. Evidence of anaemia was seen in monkeys (5 mg/kg/day PO for 28 days) and mice that received a single dose of ponatinib (450 mg/kg PO). These haematological and lymphoid organ changes have been seen previously in animal studies with dasatinib and imatinib as well as other tyrosine kinase inhibitors and have been suggested to be associated with inhibitory activity on Vascular endothelial growth factor (VEGFR), c-KIT[24], PDGFR and SRC-family kinases that have a role in haematopoiesis and/or lymphopoiesis.[25,26,27,28] The haematological changes suggest a risk for infection exists in patients. Opportunistic infections were observed in some animals that received ponatinib. Anaemia may also be seen.

The bone was a target organ in rats. In the 28 day study, minimal to mild cartilaginous hyperplasia of the growth plate was seen in the femur of animals that received ≥3 mg/kg/day PO ponatinib (ER_{AUC} 0.7). Reduced trabecular bone and reduced chondrocytes along the growth plate with islands of residual cartilage were seen in rats that received ≥0.75 mg/kg/day PO ponatinib for 6 months. These bone effects had not reversed after a 2 month treatment free period. No such bone effects were observed in Cynomolgus

[23] EMEA/CHMP/SWP/150115/2006: Reflection paper on non-clinical evaluation of drug-induced liver injury [DILI])
[24] C-Kit: a type of receptor tyrosine kinase and a type of tumor marker. Also called CD117 and stem cell factor receptor.
[25] Gerber H.P. and Ferrara N. (2003). The role of VEGF in normal and neoplastic hematopoiesis. *Journal of Molecular Medicine* **81:**20–31..
[26] Broudy V.C. (1997) Stem cell factor and hematopoiesis. *Blood.* **90:** 1345–1364.
[27] Corey S.J. and Anderson S.M. (1999) Src-related protein tyrosine kinases in hematopoiesis. *Blood.* **93:** 1–14.
[28] Kaminski W.E., Lindahl P., Lin N.L., Broudy V.C., Crosby J.R., Hellstrom M., Swolin B., Bowen-Pope D.F., Martin P.J., Ross R., Betsholtz C. and Raines E.W. (2001) Basis of hematopoietic defects in platelet-derived growth factor (PDGF)-B and PDGF β-receptor null mice. *Blood.* **97:** 1990–1998.

monkeys. Similar bone effects have been reported in rodent studies with VEGFR inhibitors. VEGF has been shown to be involved in cartilage remodelling, ossification and angiogenesis during endochondrial bone formation.[29] Therefore, the effects on bones in rats may be due to off-target inhibitory activity on VEGFR. As primate physes have minimal to no postpubertal growth (unlike the physes of rodents), these bone effects are expected to have minimal relevance to an adult patient group with closed physes.

The heart was not always consistently affected in treated animals. Systolic heart murmurs were evident in a number of monkeys that received ≥1 mg/kg/day PO ponatinib (ER_{AUC} 0.1). While there were no cardiac lesions seen in these animals, myocardial fibrosis and/or necrosis was seen in other animals (rats that received a single oral dose ≥10 mg/kg and monkeys given ≥0.25 mg/kg/day PO ponatinib for 6 months). The underlying mechanism for these cardiac changes is uncertain. Cardiac fibrosis was reported in previous animal studies with dasatinib and haemodynamic changes are known with VEGFR inhibitors. Nonetheless, the data indicates the risk of heart murmurs and myocardial damage during clinical use with ponatinib.

One male monkey (of three) that received 5 mg/kg/day PO ponatinib for 28 days (ERAUC 6) had minimal germ cell degeneration characterised by a slight decrease in the number of spermatids in some seminiferous tubules as well as infrequent spermatid giant cells. Germinal epithelial degeneration was still seen in one of two male monkeys after a 4 week treatment free period. While these testicular effects may be attributed to stress and a generally deteriorating condition, a drug-related effect cannot be dismissed. c-KIT and c-SRC, targets of ponatinib, are known to be involved in spermatogenesis and testis physiology[30, 31, 32] and therefore, it is mechanistically plausible that these effects are a direct pharmacological effect of ponatinib. Increased ovarian follicular atresia was seen in female monkeys that received 5 mg/kg/day PO ponatinib for 28 days (ERAUC 6; ERAUC at the No Observable Effect Level (NOEL) 1.2). The lack of significant follicle development resulted in atrophy of the uterine endometrium. VEGFR is known to have a role in the development and function of the corpus luteum[33, 34]. Effects on follicular development have been reported previously with VEGFR inhibitors and therefore this effect may be attributable to off-target activity on VEGFR. Some impairment of fertility (both male and female) may be seen with ponatinib.

Effects on the coagulation system were evident in rats and monkeys. Haemorrhage was observed on occasion in various tissues of rats that received ≥1.5 mg/kg/day PO ponatinib and there was an increase in activated partial thromboplastin time (APTT) and prothrombin time (PT) (14 day study only) in Cynomolgus monkeys that received ≥5 mg/kg/day PO ponatinib. No studies were conducted to specifically assess effects on platelet function. Haemorrhages and prolonged bleeding time were reported in animal studies with dasatinib (EPAR for dasatinib). Various SRC-family kinases are involved in

[29] Gerber H.P., Vu T.H., Ryan A.M., Kowalski J., Werb Z. and Ferrara N. (1999). VEGF couples hypertrophic cartilage remodeling, ossification and angiogenesis during endochondral bone formation. *Nat Med.* **5:** 623-628.
[30] Nishio H., Tokuda M., Itano T., Matsui H., Takeuchi Y. and Hatase O. (1995) pp60c-src expression in rat spermatogenesis. *Biochem. Biophys. Res. Commun.* **206:** 502–510.
[31] Sandlow J.I., Feng H.L. and Sandra A. (1997) Localization and expression of the c-kit receptor protein in human and rodent testis and sperm. *Urology.* **49:** 494–500.
[32] Prabhu S.M., Meistrich M.L., McLaughlin E.A., Roman S.D., Warne S., Mendis S., Itman C. and Loveland K.L. (2006) Expression of c-Kit receptor mRNA and protein in the developing, adult and irradiated rodent testis. *Reproduction.* **131:** 489–499.
[33] Ferrara N., Chen H., Davis-Smyth T., Gerber H.P., Nguyen T.N., Peers D., Chisholm V., Hillan K.J. and Schwall R.H. (1998) Vascular endothelial growth factor is essential for corpus luteum angiogenesis. *Nat. Med.* **4:** 336–340.
[34] Pauli S.A., Tang H., Wang J., Bohlen P., Posser R., Hartman T., Sauer M.V., Kitajewski J. and Zimmermann R.C. (2005) The vascular endothelial growth factor (VEGF)/VEGF receptor 2 pathway is critical for blood vessel survival in corpora lutea of pregnancy in the rodent. *Endocrinology.* **146:** 1301–1311.

signal transduction pathways mediating platelet activation.[35] As ponatinib has inhibitory activity on the SRC-family kinases, the effects on the coagulation system are likely pharmacologically mediated. The data indicates the possibility of bleeding episodes and haemorrhage in patients taking ponatinib. Coagulation parameters should be monitored during clinical use.

The thyroid gland was a target organ in monkeys. Minimal to moderate follicular atrophy was seen in monkeys that received ≥2.5 mg/kg/day PO (ERAUC 1.2) for 28 days, or single oral doses ≥5 mg/kg. Changes in thyroid hormone levels correlated with the histological findings, with reduced levels of triiodothyronine(T_3) and increased levels of thyroxine (T_4) seen in males and an increase in Thyroid stimulating hormone(TSH) levels seen in females that received 5 mg/kg/day PO ponatinib. Recovery was incomplete after a 4 week treatment-free period. There were no thyroid effects observed in rats, though reduced thyroid weights were seen in mice that received single high oral doses of ponatinib (≥50 mg/kg) (histopathological analyses were not performed). The underlying mechanism for the thyroid changes is unknown. Some thyroid changes were seen in animals treated with dasatinib and imatinib but the lesions were dissimilar to those reported here. The findings from ponatinib treated monkeys indicate some thyroid effects may be seen in patients.

The pancreas was a target organ for toxicity in Cynomolgus monkeys but not in rats. Elevated serum lipase levels (by 8 times) were observed in monkeys that received 5 mg/kg/day PO ponatinib for 28 days. Diffuse, moderate acinar cell necrosis accompanied by diffuse interstitial fibroplasia was evident microscopically in monkeys that received ≥2.5 mg/kg/day PO for 28 days (ERAUC 1.2). One monkey that received 2 mg/kg/day PO ponatinib for 14 days had pancreatitis. No pancreatic lesions were evident after a 2 month treatment-free period. The mechanism underlying the pancreatic effects in Cynomolgus monkeys only is unknown. Pancreatic lesions were not observed in animal studies with others in the pharmacological class but they have been reported in studies with VEGFR inhibitors. It is noted that pancreatitis was a dose limiting toxicity in the clinical studies, thus confirming the findings in monkeys are clinically-relevant.

Skin erythema was observed in all species at high single and moderate to low repeated oral doses of ponatinib. This may be attributable to the effects of ponatinib on the coagulation system (similar to that with other members of this pharmacological class), or it may be associated with a hypersensitivity reaction. Seborrhoea, dry, flaky skin, skin (serocellular) crusts and/or hyperkeratosis were observed in female rats (at ≥0.75 mg/kg/day PO for 6 months; ERAUC 0.3) and monkeys (at 5 mg/kg/day for 28 days; ERAUC 6). The skin changes were obvious after 5 days of dosing to monkeys. Scratching was observed in some animals. Skin crusts and dry flaky skin were not observed in the 6 month monkey study, likely due to the low exposures achieved in this study. The dry, flaky skin resolved 5 to 12 days after cessation of treatment in monkeys but complete reversibility was not seen in rats after a 2 month treatment-free period. The mechanism underlying the skin changes is unknown. There have been similar reports of rashes in human subjects taking ponatinib, confirming the findings in animals have clinical significance.

In the 6 month rat study, focal adrenocortical necrosis was seen at the high dose in females (2 mg/kg/day PO; ERAUC 1.0). No adrenal effects were observed in the shorter term rat studies or in any of the monkey studies at higher exposures (at least in studies ≤28 days). Adrenal lesions have not been seen with other BCR-ABL inhibitors. Given the lack of consistency across species, across sexes and across studies, the adrenal changes are considered to have minimal clinical relevance.

[35] Gibbins J.M. (2004) Platelet adhesion signalling and the regulation of thrombus formation. *J. Cell Sci.* 117:3415–3425.

An increased incidence and severity of chronic progressive nephropathy (CPN) was seen in rats (≥0.75 mg/kg/day PO; females at 2 mg/kg/day PO). No renal lesions were seen in monkeys at higher exposures. While the increase in CPN may be drug-related, such an effect in rats is not generally considered a predictor of renal toxicity in humans.[36]

Genotoxicity

The genotoxic potential of ponatinib was assessed in the standard battery of tests. All studies were adequately conducted under GLP conditions. Ponatinib was not mutagenic in an Ames test and was not clastogenic in vitro (in human lymphocytes) or in vivo (mouse micronucleus study). As the metabolite, AP24600, is not formed in rat microsomes, the genotoxic potential of this metabolite has not been assessed in the above in vitro studies. Adequate exposure would have been achieved in the micronucleus test. Ideally, in vitro genotoxicity studies with AP24600 should have been conducted but the absence of such studies is not considered a major deficiency, in light of the negative in vivo findings and considering the intended patient group.

Carcinogenicity

No carcinogenicity studies were conducted, which is considered acceptable, given the intended patient group.[37]

Reproductive toxicity

Reproductive toxicity studies with ponatinib were restricted to assessments on the effects on embryofetal development in rats. This is considered acceptable given the proposed indication.[37] In the general toxicity studies, the male and female reproductive organs were target organs for toxicity and reduced fertility may be seen in patients (see *Repeat-dose toxicity*).

In the pivotal embryofetal development study, adequate animal numbers were used and treatment periods were appropriate. Maximum exposures achieved, however, were low being at or below the clinical AUC (Table 4). Nonetheless, the highest dose was clearly toxic to the dams (maternotoxic).

Table 4. Relative exposure in the pivotal embryofetal development study

Species	Study	Dose (mg/kg/day)	$AUC_{0-24\,h}$ (µg·h/mL)[#]	Exposure ratio[#]
Rat (SD)	Embryofetal development [Study 20009232]	0.3	0.036	0.03
		1	0.314	0.3
		3	1.28	1.1
Human	–	[45mg]	1.20	–

[#]GD17 data for rats

Ponatinib was embryofetal lethal, embryofetotoxic and teratogenic in rats at clinical or subclinical exposures. An increase in postimplantation loss was observed at 3 mg/kg/day PO, resulting in a lower number of live fetuses. Decreased fetal body weights and gross

[36] Hard G.C., Johnson K.J. and Cohen S.M. (2009) A comparison of rat chronic progressive nephropathy with human renal disease – implications for human risk assessment. *Crit. Rev. Toxicol.* **39:** 332–346.
[37] EMEA/CHMP/ICH/646107/2008 Note for guidance on nonclinical evaluation for anticancer pharmaceuticals.

fetal external changes (whole body oedema, abdominal distention, short tail and cleft palate) were also seen at this dose. Fetal abnormalities included alterations in the fetal soft tissue morphology (predominantly to the vessels and the urogenital system) and skeletal changes (fused, irregularly shaped limbs/vertebrae, incomplete ossification). A reduced number of ossification sites were seen in fetuses from dams that received 3 mg/kg/day PO ponatinib. Fetal abnormalities were observed at a non-maternotoxic dose (1 mg/kg/day PO; skeletal variations only) but the majority were seen in fetuses from dams that received 3 mg/kg/day PO ponatinib. In general, the embryofetal findings with ponatinib are similar to those seen in animal embryofetal development studies with others in the pharmacological class and VEGFR inhibitors. Therefore, as with others in the class, ponatinib should only be used during pregnancy if there is a clear benefit to the mother that would warrant the risk to the developing fetus.

Pregnancy classification

The sponsor has proposed Pregnancy Category D.[38] This is considered appropriate given the malformations observed in the embryofetal development studies.

Immunotoxicity

Lymphoid depletion observed in repeat-dose toxicity studies, indicates a risk for opportunistic infections during clinical use.

Phototoxicity

There was no evidence of cutaneous phototoxicity in pigmented rats that received a single dose at ≤10 mg/kg PO ponatinib (estimated exposures 7 times the clinical AUC and 9 times the clinical C_{max}). However, ocular phototoxicity was evident at 5 and 10 mg/kg, consisting of diffuse superficial corneal oedema, corneal scar and lenticular epithelial hyperplasia. The NOEL for ocular phototoxicity was 2.5 mg/kg PO resulting in estimated exposures similar to the clinical exposure (estimated C_{max} 63 ng/mL; estimated AUC 1.0 µg.h/mL). The ocular findings in animals indicate routine monitoring of patients for ocular defects may be warranted.

Impurities

The proposed specifications for two impurities in the drug substance are above the relevant qualification threshold. One of these is a significant metabolite in rodents and humans. It is however controlled in the drug product at levels below the qualification threshold and therefore no further qualification was required. The proposed limit for the other impurity had at the time of this report not been adequately qualified based on toxicological data.

Paediatric use

Ponatinib is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary

- The submitted nonclinical data were in accordance with the relevant TGA adopted EU guideline for the nonclinical assessment of anticancer pharmaceuticals.[37] The overall quality of the dossier was high with all pivotal safety studies conducted under GLP conditions.

[38] Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

- In vitro, ponatinib reduced the viability of cells expressing native BCR-ABL or its mutant variants that are relatively resistant to imatinib, nilotinib and/or dasatinib. Efficacious concentrations were within clinical plasma levels. Tumour regression was observed in mice bearing SC allografts or xenografts of cells expressing the native BCR-ABL or the imatinib/nilotinib/dasatinib-resistant BCR-ABL mutant, T315I, while prolonged survival was seen in mouse CML models (native BCR-ABL or its T315I mutant). Efficacious doses/exposures were similar to or slightly greater than that anticipated clinically. Ponatinib was clearly less efficacious in models expressing the T315I mutant than those expressing the native BCR-ABL. In general, the data support the proposed indication. Based on in vitro data, ponatinib may be less efficacious in patients carrying the E255K/V mutations.
- Ponatinib had inhibitory activity at RET, FLT3, KIT and members of the FGFR, PDGFR, VEGFR, EPH and SRC families of kinases at clinically-relevant concentrations.
- Safety pharmacology studies assessed effects on the cardiovascular, respiratory, renal, and gastrointestinal and central nervous systems. No adverse effects were seen on CNS function in mice, respiratory, gastrointestinal or renal function in rats. A decrease in gastric emptying and a diuretic effect were seen in rats at clinically relevant exposures. No significant inhibition of hERG K^+ channel tail current was observed at clinically-relevant concentrations. Ponatinib is not predicted to prolong the QT interval in patients. Heart murmurs, with an unknown underlying cause, were seen in monkeys at subclinical plasma levels.
- Oral bioavailability was moderate in rats and low in Cynomolgus monkeys. Some pre-systemic metabolism was indicated. Protein binding was high in the plasma of animals and humans. Tissue distribution studies in rats indicated a specific binding and retention of drug-related material to the uveal tract. Metabolism of ponatinib was moderate to extensive in animals and humans, with major roles of CYP3A4 and 2C8 in the formation of oxidative metabolites. The main human carboxylic acid metabolite (AP24600) was a significant metabolite in rodents. Excretion of ponatinib and/or its metabolites was predominantly by the biliary/faecal route in animals and humans.
- Based on in vitro studies, CYP3A4 inhibitors/inducers and possibly CYP2C8 inhibitors could alter the systemic exposure to ponatinib. Ponatinib is not expected to alter the exposure of co-administered drugs that are CYP450 substrates. Ponatinib may increase the exposure of co-administered drugs that are substrates of P-glycoprotein or BCRP.
- Single-dose toxicity studies in mice, rats and Cynomolgus monkeys indicated a moderate to high order of toxicity.
- Repeat-dose toxicity studies by the oral route were conducted in mice (2 weeks), rats (up to 6 months) and Cynomolgus monkeys (up to 6 months). Maximum exposures (AUC) were low in rats while more acceptable exposures were achieved in shorter term monkey studies. Target organs for toxicity were the liver (reversible elevations in ALT and AST with occasional hepatocellular necrosis evident in post-mortem analyses), lymphoid organs (lymphoid depletion of the thymus, spleen, lymph nodes and/or GALT), bone (aberrant cartilage synthesis and bone formation), heart (heart murmurs and myocardial fibrosis/necrosis), reproductive tissues (hypospermia and increased ovarian follicular atresia), thyroid gland (altered hormones and follicular atrophy), pancreas (acinar cell necrosis and pancreatitis), skin (erythema and dry flaky skin), adrenal gland (adrenocortical necrosis) and kidney (chronic progressive nephropathy). Anaemia and impairment of the coagulation system (increased activated partial thromboplastin time (APTT) and prothrombin time (PT) with evidence of haemorrhage) were also seen.

- Ponatinib was not mutagenic in an Ames test and was not clastogenic in vitro (in human lymphocytes) or in vivo (mouse micronucleus study). No carcinogenicity studies were conducted, which is considered acceptable.
- Reproductive toxicity studies with ponatinib were restricted to assessments on the effects on embryofetal development in rats. Ponatinib was embryofetal lethal, embryofetotoxic and teratogenic (soft tissue abnormalities and skeletal changes) in rats at clinical or subclinical exposures.
- Ocular phototoxicity (diffuse superficial corneal oedema, corneal scar and lenticular epithelial hyperplasia) was seen in pigmented rats. Estimated exposure at the NOEL was similar to the clinical exposure.
- The proposed limit for one impurity in the drug substance has not been adequately qualified by submitted toxicity data.

Nonclinical conclusions and recommendation

The primary pharmacology studies generally support the proposed use of ponatinib as an oral agent for the treatment of patients with CML or Ph+ ALL that is resistant to imatinib, dasatinib or nilotinib, though efficacy will be somewhat dependent on the BCR-ABL mutation present.

The combined animal safety studies revealed the following findings of potential clinical relevance:

- Heart murmurs and possible cardiac arrhythmias
- Hepatotoxicity
- Pancreatic damage and pancreatitis
- Immunosuppression and risks for infection
- Anaemia
- Haemorrhages and bleeding episodes
- Changes in thyroid hormones and thyroid effects
- Skin lesions
- Photo-ocular damage

Provided the above effects are adequately monitored or managed during clinical use and the benefit/risk profile seems acceptable from a clinical perspective, there are no objections on nonclinical grounds to the proposed registration of Iclusig.

Amendments to the draft Product Information were also recommended but the details of these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Orphan drug designation

Ponatinib was designated as an orphan drug by the TGA on 14 May 2013. The indication for which orphan designation was granted was:

> *For the treatment of acute lymphoblastic leukaemia and adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) that is resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy.*

Comment: The orphan designation includes all subjects with ALL, whereas the indication proposed for registration is restricted to Ph +ve ALL.

For both ALL and CML, the orphan designation includes patients who have only failed imatinib, the first-generation BCR-ABL TKI. However these subjects have been excluded from the indication proposed for registration, which requires that subjects must have failed therapy with one of the second-generation agents (dasatinib or nilotinib).

The indication proposed for registration includes subjects with the T315I mutation. It is theoretically possible that some subjects in this group may not have yet failed prior TKI therapy when the mutation is detected. These subjects are not covered by the orphan designation.

Clinical rationale

The BCR-ABL protein produced by the t(9,22) translocation has a kinase domain. The kinase function is unregulated and it causes constitutive activation of mitogenic signals, reduced apoptosis and altered adhesion properties in affected cells.[39] Inhibition of the TKI activity is intended to impair the disease process. Other BCR-ABL TKIs (imatinib, dasatinib, nilotinib) have been shown to have substantial clinical activity in CML and Ph+ve ALL.

Resistance to currently available BCR-ABL TKIs can occur. The most common mechanism of resistance is the development of mutations in the kinase domain of the BCR-ABL protein. A large number of such mutations have been described. One such mutation is the substitution of threonine at position 315 of the molecule with isoleucine (T315I). This particular mutation renders the BCR-ABL molecule resistant to all currently available BCR-ABL TKIs.[40] The purported advantage of ponatinib is that it is effective in subjects who are resistant or intolerant to currently available BCR-ABL TKIs, including subjects who have the T315I mutation.

A summary of the approved indications for registered BCR-ABL TKIs and the proposed indications for ponatinib is given in Table 1above.

Guidance

The following EU guidelines, which have been adopted by the TGA, are considered relevant to the submission:

[39] Deininger MWN, Goldman JN and Melo JV. The molecular biology of chronic myeloid leukaemia. *Blood*; 2000 November; 96(10): 3343-3356.
[40] Quintas-Cardama A and Cortes J. Molecular biology of bcr-abl1-positive chronic myeloid leukaemia. *Blood*; 2009 February; 113(8): 1619-1630.

- Guideline on anticancer medicinal agents[41];
- Appendix 2 to the guideline on anticancer medicinal agents[42], which is concerned with trials in haematological malignancies.

Compliance with these guidelines is considered in the relevant sections of this report.

Contents of the clinical dossier

Scope of the clinical dossier

The clinical dosser documented a full clinical development program of pharmacology, efficacy and safety studies. The submission contained the following clinical information:

- Three Phase I pharmacokinetic studies conducted in healthy volunteers (Studies 102, 103 and 104)
- One Phase I study in patients with haematological malignancies, which examined pharmacokinetics, efficacy and safety (Study 101)
- One pivotal Phase II efficacy and safety study (Study 201) in patients with CML/Ph+ve ALL
- One population pharmacokinetic analysis of PK data collected from 3 of the Phase I studies
- Two post-marketing reports
- Literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The clinical study reports for the submitted studies included assurances that the studies were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation (ICH) Good Clinical Practices (GCP).

Pharmacokinetics

Studies providing pharmacokinetic data

Table 5 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 5: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	Mass balance (^{14}C radiolabelled drug)	Study 104

[41] European Medicines Agency. Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95/Rev.3/Corr.); 2005. Available from: http://www.tga.gov.au/pdf/euguide/ewp020595enrev3.pdf
[42] European Medicines Agency. Appendix 2 To The Guideline On The Evaluation of Anticancer Medicinal Products In Man: Confirmatory studies in Haematological Malignancies (EMA/CHMP/EWP/520088/2008); 2010. Available from: http://www.tga.gov.au/pdf/euguide/chmp52008808enfin.pdf

PK topic	Subtopic	Study ID
	Food effect	Study 102
PK in target population	Single dose and multiple dose	Study 101
PK interactions	Ketoconazole (CYP 3A4 inhibitor)	Study 103
Population PK analyses	Healthy subjects & target population (Data from studies 101, 102, 103)	-

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

In general, the pharmacokinetics of ponatinib have been adequately investigated. There are two significant deficiencies in the submitted PK data:

- The absolute bioavailability of ponatinib has not been defined; and
- There are no adequate data on the PK of ponatinib in subjects with hepatic impairment.[43]

Pharmacodynamics

Studies providing pharmacodynamic data

Only one of the submitted studies (Study 101) provided pharmacodynamic data. It examined the effect of ponatinib on levels of phosphorylated CRK[44] like (pCRKL) in peripheral blood mononuclear cells of patients with CML or Ph+ALL. pCRKL is an adapter protein for BCR-ABL, and measurement of pCRKL levels can be used as a surrogate for measuring BCR-ABL activity in vivo.

Evaluator's conclusions on pharmacodynamics

The study demonstrated that ponatinib reduced pCRKL levels consistent with inhibition of BCR-ABL activity.

Dosage selection for the pivotal studies

The starting dose of 45 mg per day was selected because it was the maximum tolerated dose in the first in man study.

[43] During the evaluation process, Study AP24534-12-109: Evaluation of Pharmacokinetics and Safety of ponatinib in Patients with Chronic Hepatic Impairment and Matched Healthy Subjects was submitted to the TGA.

[44] CRKL is expressed in hematopoietic cells and has been implicated in pathogenesis of chronic myelogenous leukemia. However, its function has not been precisely defined.

Efficacy

Studies providing efficacy data

The following studies provided efficacy data:

- One Phase I study in patients with haematological malignancies, which examined pharmacokinetics, efficacy and safety (Study 101)
- One pivotal Phase II efficacy and safety study (Study 201) in patients with CML/Ph+ve ALL;

Evaluator's conclusions on efficacy

The sponsor has provided efficacy data from two open-label, non-comparative studies. The patients included in these studies were heavily pre-treated with currently registered TKIs. The studies used standard endpoints for determination of efficacy in CML and Ph+ve ALL.

For patients in chronic phase CML, a major cytogenetic response was achieved in 53.9% in Study 201 and 72.1% in Study 101. The higher response rate in Study 101 may reflect longer duration of follow up. The responses appeared durable, with median duration of response not being reached in either study.

For patients in accelerated phase CML, a major haematological response was achieved in 57.8% in Study 201. Responses were less durable, with median durations of response being 5.7 to 9.5 months.

Efficacy was less impressive in subjects in blast phase CML and Ph+ acute lymphocytic leukaemia, with rate of MaHR being approximately 30 to 40% and with responses being short-lived (median of 4.1 months in Study 201).

The most notable findings from these studies are that efficacy has been demonstrated in:

- Subjects for whom currently available TKIs have failed
- Subjects who harbour the T315I mutation in BCR-ABL, which is associated with resistance to currently available TKIs.

Overall, the data are considered adequate to establish the efficacy of ponatinib.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

- Pivotal efficacy study (Study 201)
- Supportive efficacy study (Study 101)
- Clinical pharmacology studies
  - The three clinical pharmacology studies (Studies 102, 103 and 104) provided very limited data on safety as they all involved the administration of single doses of ponatinib to healthy volunteers.
- Pooled safety database

In the submission, the sponsor presented analyses of safety based on pooled data from Studies 101 and 201. The pooled safety data has been used in this report for the purposes of assessing safety.

There were three reports presented for the pooled safety database:

- The sponsor's Summary of Clinical Safety which included safety data collected up to the data cut-off dates for the two studies (23 March 2012 for Study 101 and 27 April 2012 for Study 201)
- A '120-day update' which included safety data collected up to 23 July 2012
- A further update included data collected up to 3 September 2013. This update focussed on vascular adverse events but also included some data on cardiac failure, ocular toxicities and neuropathy.

There were no studies in the submission designed to assess safety as a primary outcome.

Patient exposure

In the five submitted clinical studies, a total of 530 patients and 53 healthy volunteers received at least one dose of ponatinib (Table 6). Of the 530 patients, 514 had CML or Ph+ALL (the proposed indication) and 16 subjects (all in Study 101) had other haematological malignancies. The pooled safety database included all 530 patients.

Table 6: Exposure to ponatinib in clinical studies.

	Healthy volunteers	Patients
Clinical Pharmacology studies		
102	24	-
103	23	-
104	6	-
Efficacy studies		
101	-	81
201	-	449
Totals	53	530

The median duration of treatment was 323 days (10.6 months). A total of 349 subjects had been treated for at least 6 months and 185 subjects for 12 months. A total of 51.5% of subjects had required dose reduction, with the median daily dose being 36.5 mg as opposed to the starting daily dose of 45 mg.

Safety issues with the potential for major regulatory impact

Liver toxicity

The two clinical studies submitted did not suggest that ponatinib would be likely to produce severe drug-induced liver injury (DILI). However it appears that at least one case of severe DILI has been reported from another study and the sponsor should be requested to provide further information on this issue.

Haematological toxicity

Myelosuppression is a very common toxicity of ponatinib. Myelosuppression events reported with the drug in the pooled safety database included 10 cases of pancytopaenia and two cases of bone marrow failure.

Serious skin reactions

At the time of the cut-off for the 120-day safety update, there were no reports of serious skin toxicity such as Stevens Johnson syndrome or toxic epidermal necrolysis.

Cardiovascular safety

Vascular adverse events are a major toxicity associated with ponatinib. The cardiac safety of ponatinib has been discussed in the clinical evaluation report (Attachment 2).

Unwanted immunological events

'Drug hypersensitivity' was reported in 3 subjects (0.6%) in the pooled safety database. Two of these events were Grade 1 in severity and the other was Grade 3. There was also one report of Grade 1 'hypersensitivity'. There was also 1 report of serious graft versus host disease. There were no other serious adverse events (AEs) of an immunological nature. These data suggest that serious immunological events due to ponatinib are uncommon.

Postmarketing data

The sponsor included two Periodic Adverse Drug Experience Reports (PADERs). Each covered a 3 month period after the initial US approval in December 2012.

- PADER #1 covered the period 14 December 2012 to 14 March 2013
- PADER #2 covered the period 15 March 2013 to 14 June 2013.

In the PADER #1 there were 44 reports of serious adverse events. These reports originated from ongoing clinical trials, compassionate use programs and post-marketing surveillance. The pattern of adverse events was consistent with that seen in the pooled safety data from Studies 101 and 201. There were several arterial vascular events (myocardial infarction, acute coronary syndrome, cerebral infarction, cerebrovascular accident and peripheral vascular disease) and venous vascular events (renal vein thrombosis, jugular vein thrombosis and retinal vein thrombosis). Other AEs that were reported were neuropathies, abnormal liver function tests (LFTs), abnormal pancreatic enzymes and skin disorders. There was one report of a fatal drug-induced fulminant hepatitis.

In the PADER #2 there were 120 reports of serious adverse events. The pattern of these events was again generally consistent with that seen in the pooled safety analysis. There were multiple reports arterial and venous vascular AEs and several reports of neuropathy events, pancreatitis, abnormal LFTs, hypertension, bleeding events, arrhythmias (mainly atrial fibrillation /flutter or tachycardia), fluid retention events, infections and cytopaenias. There were 10 cases of renal impairment/failure. Four of these subjects had plausible alternative aetiologies.

Evaluator's conclusions on safety

The safety profile of ponatinib has many similarities to other BCR-ABL TKIs. The following toxicities observed with ponatinib have previously been associated with this class of drugs:

- Myelosuppression and infections

- Bleeding events
- Pancreatic toxicity
- Hepatotoxicity
- Cardiac failure and reduced LVEF
- Fluid retention events
- Hypertension
- Dermatological toxicity
- Gastrointestinal toxicity.

Also, QT prolongation due to ponatinib has not been excluded.

Compared to other agents in the class, ponatinib is associated with a high incidence of vascular adverse events, especially arterial (ischaemic) events. Subjects with pre-existing risk factors for ischaemia are particularly at risk of ischaemic events.

The overall toxicity of the drug is significant, with a high proportion of patients experiencing serious adverse events and Grade 3 or 4 adverse events. Approximately 1% of patients died due to adverse events that were considered related to ponatinib. Despite the high incidence of adverse events, the incidence of discontinuation of ponatinib due to adverse events was comparatively low. This suggests that the toxicities produced by the drug could be managed in most patients (for example with dose reductions, drug interruptions and supportive therapies).

There are some outstanding questions regarding the incidence of vascular events and the possibility that the drug may be associated with severe drug induced liver injury.

First round benefit-risk assessment

First round assessment of benefits

The benefits of ponatinib in the proposed usage are:

- The induction of a major cytogenetic response in a substantial proportion of treated subjects (53.9% in chronic phase, 38.6% in accelerated phase, 22.6% in blast phase and 46.9% in Ph+ALL)
- The induction of a major haematological response in a substantial proportion of subjects with advanced disease (57.8% in accelerated phase, 30.6% in blast phase and 40.6% in Ph+ALL).

The responses obtained appear to be durable, especially in chronic and accelerated phase disease. It is of particular importance that these benefits have been demonstrated in a population of subjects who:

a. Have exhausted the currently available options for treatment with a BCR-ABL TKI; or

b. Have the T315I mutation in BCR-ABL, which is known to confer resistance to currently available BCR-ABL TKIs.

As the efficacy data come from two non-comparative studies, it is not possible to conclude that the drug is associated with any benefits in terms of survival or progression-free survival. Effects on quality of life were not studied.

First round assessment of risks

The risks of ponatinib in the proposed usage are:

- A risk of significant toxicity, with serious AEs occurring in 56.2% of subjects (treatment-related 22.6%), Grade 3 or 4 adverse events occurring 67.7% and treatment related deaths occurring in approximately 1% of subjects.

The pattern of toxicity is generally consistent with that with other drugs in the same class. However, ponatinib is associated with a notably increased risk of vascular adverse events. It also appears that the drug may be associated with a risk of severe drug-induced liver injury.

Despite a high incidence of adverse events, the incidence of discontinuation due to adverse events was modest (17.9%; treatment-related 8.3%), suggesting that the toxicity of the drug was manageable in most patients.

First round assessment of benefit-risk balance

The safety concerns associated with ponatinib are significant. In particular, the high incidence of vascular events suggests that the drug may be more toxic than currently available BCR-ABL TKIs. On the other hand, the drug has substantial efficacy and the proposed population is effectively one in which the other BCR-ABL TKIs cannot be used.

Alternative treatments for those subjects who have failed dasatinib or nilotinib, or those who have the T315I mutation are limited.

- Allogeneic stem cell transplantation (ASCT) would be a suitable treatment in some patients. However it is a procedure associated with significant morbidity and mortality and it is not possible to conclude that it would produce more favourable outcomes than ponatinib. In patients eligible for ASCT, drug treatment has been shown to produce better survival outcomes than ASCT, at least in the first-line setting.[45] ASCT is considered to be the treatment of choice for patients with blast phase or accelerated phase disease.[46,47] In heavily pretreated patients such as those enrolled in the submitted studies, the possibility of performing ASCT is likely to have already been considered. It is noted that approximately 20% of blast phase subjects and 10% of accelerated phase patients in Study 201 had already undergone stem cell transplant. ASCT would not be an option for many patients because of co-morbidity or lack of a suitable donor.
- Prior to the introduction of BCR-ABL TKIs, interferon-based therapy was considered to be the most effective treatment for chronic phase CML. However, in a randomised controlled trial of the interferon-based therapy versus imatinib in the first-line setting, the Major Cytogenetic Response (MCyR) rate with interferon was 22.1% (compared with 85.2% in the imatinib arm).[48] In Study 201 the MCyR rate with ponatinib in chronic phase CML was 53.9%. It therefore seems likely that ponatinib would be more effective than interferon. Interferon therapy is also associated with significant toxicity.

[45] Hehlmann R, Berger U, Pfirrmann M et al. Drug treatment is superior to allografting as first-line therapy in chronic myeloid leukemia. *Blood*; 2007; 109 (11): 4686-4692.
[46] Gratwohl A and Heim D. Current role of stem cell transplantation in chronic myeloid leukaemia. *Best Pract Res Clin Haematol*. 2009 September; 22 (3): 431-43.
[47] Benyamini N and Rowe JM. Is there a role for allogeneic transplantation in chronic myeloid leukemia? *Expert Rev Hematol*. 2013 December; 6(6): 759-65.
[48] O'Brien SG, Guilhot F, Larson RA, et al. Imatinib Compared with Interferon and Low-Dose Cytarabine for Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia. *N Engl J Med;* 2003; (348): 994-1004.

- Other agents such as omacetaxine (homoharringtonine) and the BCR-ABL TKI bosutinib have shown efficacy in subjects who have failed prior BCR-ABL TKI therapy. However, these agents are not registered in Australia.

Given the lack of available treatment options for the proposed population and the seriousness of the conditions being treated, it is considered that the benefits of ponatinib outweigh the risks associated with its use. The benefit-risk balance of ponatinib, given the proposed usage, is therefore considered favourable.

As the drug is intended for the treatment of a life-threatening condition for which the available treatment options are limited, the data deficiencies in the submission (absolute bioavailability study, PK study in hepatic impairment) should not preclude approval.

The proposed indication should be revised, as discussed below.

First round recommendation regarding authorisation

Subject to the provision of additional safety data (see *Clinical questions* below), it is recommended that the application be approved.

Clinical questions

General

1. According to its website[49], the EMA has raised a series of questions regarding ponatinib with a response due by 3 March 2014. Please provide a copy of these responses.

Pharmacokinetics

2. Please provide an update on the progress of the planned study in subjects with hepatic impairment.

Safety

3. The addendum to the clinical overview (data cut-off 3 September 2013) only provided updated data on vascular adverse events from Study 201. It is noted that the US prescribing information indicates that the incidence of vascular AEs in Study 101 was 48%, which is much higher than that reported for Study 201. Please provide updated data on vascular AEs from Study 101.
4. The 120 day safety update refers to a case of fatal hepatic failure, meeting the criteria for Hy's law, which occurred in a Phase I/II study in Japanese subjects. Please provide further details of this case. It is also noted that the US prescribing information refers to two other cases of fatal hepatic failure. Please provide details of these cases. Please advise whether any other cases meeting Hy's law criteria, or cases of hepatic failure, have been observed.
5. In Study 101, testing of coagulation parameters, cardiac troponins and TSH were planned. Analyses of the results of these parameters could not be located in the submission. Please comment.

[49] EMA/PRAC/746091/2013 List of questions to be addressed by the marketing authorisation holder in writing <http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Iclusig_20/Procedure_started/WC500157072.pdf>

6. Please provide the available safety data from the discontinued EPIC study.

Second round evaluation of clinical data submitted in response to questions

The sponsor's response to the above questions was dated 13 June 2014. The responses submitted by the sponsor and the evaluator's comments on these responses are shown in Attachment 2: Extract from the CER.

Second round benefit-risk assessment

Second round assessment of benefits

No significant new clinical information on efficacy was submitted in response to questions. Accordingly, the benefits of ponatinib are unchanged from those identified in the First round evaluation.

Second round assessment of risks

The responses to clinical questions have clarified that hepatic failure and heart failure are additional risks associated with ponatinib. In addition, the responses have provided further detail on the risk of vascular adverse events.

Second round assessment of benefit-risk balance

Given the proposed patient population and the lack of available alternatives, the risk-benefit balance of ponatinib for the revised indication is still considered favourable.

Second round recommendation regarding authorisation

It is recommended that the application be approved.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP, version 6, dated 12 November 2013 and an Australian Specific Annex, version 2, dated 25 November 2013 and EU-RMP, version 9.0, dated 4 June 2014, data lock point 6 January 2014which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 18.

Table 18: Summary of ongoing safety concerns

Summary of safety concerns	
Important identified risk	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 Ischemic cardiac events Ischemic cerebrovascular events Ischemic peripheral vascular events ARIAD proposes to create Brochures for the patient and the HCP as well as a patient Alert Card (see Annex 11). A DHCP communication will also be performed to provide recommendation to the prescribers on the arterial thrombotic events risks.
Important potential risks	Bleeding Hypophosphataemia and related symptoms Pulmonary hypertension Teratogenicity Off-label use Peripheral neuropathy Cranial Neuropathy Retinal vascular events
Important missing information	Treatment with ponatinib > 24 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 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 Treatment of paediatric patients

Pharmacovigilance plan

Routine pharmacovigilance activities are proposed for all ongoing safety concerns. Additional pharmacovigilance activities are proposed for:

1. The important potential risk of Teratogenicity and
2. All important missing information.

Risk minimisation activities

Routine risk minimisation activities are proposed for all ongoing safety concerns except for the potential risk of pulmonary hypertension. Additional risk minimisation activities are proposed for the important identified risks of Ischemic cardiac events, Ischemic cerebrovascular events and Ischemic peripheral vascular events.

Reconciliation of issues outlined in the RMP report

Table 19 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 19: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the TGA's consolidated request for further information and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP	All safety considerations raised by the nonclinical and clinical evaluators in the consolidated request, including requests made to the RMP, have been addressed: in the framework of the responses to the requests, via updates to the EU RMP that have been occurring in the framework of variation EMEA/H/C/2695/II/005/G and the ongoing referral procedure laid down in Article 20 of regulation EC 726/2004, or in Australia-specific changes that will be made to the ASA. ARIAD will provide an updated ASA at the next review milestone as discussed on the 21 May 2014 teleconference with TGA.	The sponsor's response has been noted. Regarding an updated ASA: It is recommended that the updated ASA be submitted as soon as possible or the latest at the sponsor's Pre-ACPM response, so the ASA can be evaluated and necessary changes to the document be negotiated.
2.1a) It is recommended that the sponsor amends the table of ongoing safety concerns in EU RMP v6.0 to include these events A. QT-prolongation, B. Arrhythmias [tachycardia and atrial fibrillation] and C. Plasma exposure to metabolites) and thereby rectifies this inconsistency in the RMP.	The inconsistency of QT prolongation and arrhythmias being missing from the table of ongoing safety concerns has been corrected in EU RMP version 9.0. The missing information of plasma exposure to metabolites has now been resolved as of EU RMP version 9.0. Similarly, the clinical pharmacology study evaluating plasma samples longer than 24 hours after dosing in the human ADME study has been completed. No new metabolites were identified in plasma samples taken greater than 24 hours after dosing. Therefore, the important missing information of plasma exposure to metabolites is considered resolved and will not be added to the table of ongoing safety concerns.	This is considered acceptable by the RMP evaluator. Nevertheless, it is recommended to the Delegate to draw the attention of the nonclinical evaluator to evaluate the appropriateness of the sponsor's justification for removing the missing information of 'plasma exposure to metabolites'.
2.1b) QT prolongation and arrhythmia are recommended to be listed as identified risks (instead of potential).	ARIAD's review of available data suggests a lack of effect of ponatinib on QT prolongation; therefore, the sponsor believes this risk should remain a potential	Pending acceptance of the sponsor's justification by the Office of Medicines Authorisation, this is

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	risk. A rationale for this conclusion is provided below. Nonclinical experiments suggest that ponatinib has a low risk of prolonging QTc interval in patients administered the proposed daily clinical dose of 45 mg. Nonetheless ECG assessments have been performed in the Phase I, Phase II and Phase III clinical trials with ponatinib. Conclusion on QT Prolongation: Because nonclinical, ECG, and clinical data to date suggest a lack of effect of ponatinib on QT prolongation, the sponsor believes this does not qualify as an identified risk should remain a potential risk, as reflected in the EU RMP version 9.0. ECG monitoring will therefore continue in future research efforts; the potential risk will be upgraded to an identified risk should accumulating data support the conclusion. Regarding Arrhythmia: In conformity with EU RMP version 9.0, ARIAD proposes to maintain atrial fibrillation as a potential risk at this time. Additional data received will be reviewed to establish whether this categorization needs to be changed. RMP evaluator's comments: The quoted text is an extract of the response provided by the sponsor.	considered acceptable.
2.2) Retinal vascular events are recommended to be changed from potential to identified risks.	This category of events will be revised in a planned update to the EU RMP (subsequent to version 9.0) as follows: Retinal vascular events will be changed from an important potential to an important identified risk in the EU RMP, and ocular toxicities that are not vascular in nature will be added as an important potential risk. This update is expected to be completed post approval.	Addition of these identified and potential safety concerns in an accordingly updated RMP/ASA is considered acceptable. However, the appropriateness of proposed risk-minimisation and pharmacovigilance activities, to address these safety concerns, will be revisited once the

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
		updated RMP/ASA has been received.
2.3) Hypertension is not currently a risk; it is recommended to include it as an identified risk.	Hypertension will be added as an identified risk in a planned update to the EU RMP (subsequent to version 9.0). This update will occur post-approval.	Addition of this identified risk in an accordingly updated RMP/ASA is considered acceptable. However, the appropriateness of proposed risk-minimisation and pharmacovigilance activities, to address these safety concerns, will be revisited once the updated RMP/ASA has been received.
2.4) Bleeding is recommended to be moved from a potential to an identified risk.	Utilizing the Bleeding Standardised MedDRA Query, 25% of patients treated with ponatinib were reported to have a bleeding event in the original summary of safety and reflected in the RMP. Most events were mild or moderate in severity, with 5% of patients experiencing a serious bleeding event, with 0.4% experiencing an SAE pertaining to bleeding considered possibly or probably related to ponatinib (2 SAEs in 2 patients). Serious bleeding events were noted in a higher percentage of patients with AP-CML (9%) and BP-CML/Ph+ ALL (10%) than CP-CML (1%). Background incidence of bleeding events in patients with leukemia is generally elevated compared to the general population as haemorrhagic diathesis is disease inherent. Bleeding in patients with leukemia was found to be significantly associated with thrombocytopenia, but also with uremia, low albumin, recent bone marrow transplant and recent haemorrhage. There is an 18% incidence of bleeding events in leukemia patients undergoing active treatment. These complications commonly occur at platelet levels between 10,000 –	Pending acceptance of the sponsor's justification by the TGA's Office of Medicines Authorisation, this is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	20,000 mm^3/L. The incidence of fatal bleeding is much less with 1-3%.[50] Because haemorrhagic diathesis is a feature of leukemia, and because of the evidence of the role of disease and decreased platelet count (itself a hallmark of disease) in many of the serious bleeding events that occurred in the Phase I and Phase II ponatinib trials, the sponsor recommends to maintain bleeding as a potential risk as leukemia itself presents a possible alternative etiology of the events.	
2.5) Hypophosphatemia and related symptoms are recommended to be moved from potential to identified risks	As summarized in the EU RMP, any-grade decreases in serum phosphorus were reported in 25% of patients, with Grade 3 decreases in 7% of patients in the Phase II trial (no Grade 4 decreases were reported). Hypophosphatemia-related symptoms were not associated with these periods of decreased phosphorus, and the clinical relevance appears to be minor. Therefore, although an identified risk, the lack of clinical significance does not elevate this identified risk to 'important' [1] (ICH E2F Guideline[51]). Due to the potential for this identified risk to become important, the sponsor recommends maintaining hypophosphatemia and related symptoms as an important potential risk.	Pending acceptance of the sponsor's justification by the TGA's Office of Medicines Authorisation, this is considered acceptable.
2.6-7) Peripheral neuropathy and cranial neuropathy are recommended to be listed as identified risks (instead of potential)	In EU RMP version 6.0, the sponsor reported 13% of patients in the phase 2 trial had peripheral neuropathy and 0.4% had serious peripheral neuropathy (03 September 2013 data). The respective incidence of treatment-emergent and serious cranial neuropathy was 1% and 0.7%. All	Pending acceptance of the sponsor's justification by the Office of Medicines Authorisation, this is considered acceptable.

[50] Henke, P.K., Varga, A., De, S., Deatrick, C.B., Eliason, J., Arenberg, D.A. et al, Deep vein thrombosis resolution is modulated by monocyte CXCR2-mediated activity in a mouse model. Arterioscler Thromb Vasc Biol. 2004;24:1130–1137.
[51] EMA/CHMP/ICH/309348/2008 ICH guideline E2F on development safety update report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	serious events were reported as resolved. In their review of EU RMP version 6.0, the EMA Pharmacovigilance Risk Assessment Committee (PRAC) provided the comment that addition of peripheral neuropathy and cranial neuropathy as potential risks was not endorsed at that time (19 November 2013), and the sponsor was asked to remove this risk from the RMP. Peripheral neuropathy has been described with TKI use (Chakupurakal et al, 2011, Loriot et al, 2013 Patejdl et al, 2013, Jungnickel et al, 2004). The PRAC believed that the body of evidence at the time, including confounding factors of prior therapy (all patients in the phase 2 trial were treated with at least 1 prior TKI, and most received at least 3) and patient risk factors (almost all patients had relevant history reported, for example, diabetes, hypertension, hypertriglyceridemia, foot amputation, osteoporosis, gout, carpal tunnel syndrome, and various cardiovascular conditions), combined with the low incidence of clinically important events, did not support inclusion of peripheral or cranial neuropathy as important potential risks. Therefore, because alternate etiologies could explain many cases of neuropathy, the PRAC argued for its removal as an important potential risk. Based on this feedback and considering the data available at the time, the sponsor removed the risk from the EU RMP altogether in version 7.0, an update that is carried forward to the current EU RMP version 9.0. This category of events is being evaluated in ongoing signal detection efforts. Based on additional data, including cases in the phase 3 trial in newly diagnosed patients, and based on the class association, it will be added back as an	

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	important potential risk in a planned update to the EU RMP (subsequent to version 9.0).	
2.8) Thyroid function disorder is recommended to be included as a potential risk.	The reviewer cites the data in the RMP of 2.3% of patients having hypothyroidism and 0.3% of patients having hyperthyroidism. Thyroid function disorder as a class effect is discussed in the RMP. The retrospective study of Kim et al (2010) is cited in which the thyroid function of patients receiving imatinib, dasatinib, or nilotinib was evaluated. Among the 73 CML patients, 33 (45%) had one or more thyroid function test abnormalities during follow-up. The distribution across TKIs was 25% of patients treated with imatinib, 55% of patients treated with nilotinib, and 70% of patients treated with dasatinib. The sponsor also cites epidemiological data in which 1% to 6% of the general population is reported to have subclinical hypothyroidism, and approximately 5% of US adults are reported to have thyroid disease or be taking thyroid medication. The AEs of hypothyroidism reported in the ponatinib clinical program were grade 1 or 2 only, and no dose modifications or interruptions were required to manage them. Furthermore, thyroid stimulating hormone (TSH) was routinely evaluated in the phase 1 trial, and no clinically relevant levels of increased TSH were observed. Given the similarity of the incidence of thyroid function AEs in the ponatinib program with that of the general population, and given the much higher incidence observed with other TKIs, the sponsor does not agree that thyroid function disorder should be included as an important potential risk for ponatinib.	Pending acceptance of the sponsor's justification by the Office of Medicines Authorisation, this is considered acceptable.
2.9) Interaction of ponatinib with oral contraceptives	This interaction has been added back to EU RMP version 9.0 as	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
should be added as missing information in the table of ongoing safety concerns	missing information. Response to 3E summarizes the history of this safety concern, nonclinical studies to address it, the rationale for the inability to conduct the in vivo interaction study, why the sponsor nevertheless does not believe ponatinib will be expected to interact with oral contraceptives, and the proposed solution to address the missing information.	
2.10) Ponatinib treatment during pregnancy and in breast-feeding women should be added as missing information	Missing information is defined as gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant. Ponatinib is not recommended for treatment during pregnancy or in breastfeeding women. Furthermore, there is no way to prospectively study this population in order to ever resolve the missing information. Therefore, the sponsor will retain the warning against use in pregnant or breast-feeding women. Although treatment during pregnancy or breast-feeding is not classified in the EU RMP as missing information, the sponsor collects all data on women who do become pregnant and the female partners of male patients who become pregnant, and would report any significant findings in these populations in the PSURs.	The RMP evaluator maintains the position, that 'Ponatinib treatment during pregnancy and in breast-feeding women' should be added as missing information to the table of ongoing safety concerns in an updated RMP/ASA. Appropriate pharmacovigilance activities to monitor this missing information should be implemented.
2.11) Patients with renal impairment should be included as missing information	The human ADME study AP24534-11-104 (excretion and biotransformation of 14C ponatinib in six healthy subjects was investigated following a single target oral dose of 45 mg/100 µCi) revealed that fecal excretion accounted for elimination of 86.63% of the radioactive dose, and the amount of drug and metabolites eliminated through urine was low (5.4% of the dose). Parent ponatinib represented <1% of	As risks to the safety of patients with severe renal impairment cannot be excluded, it is recommended that 'safety in patients with severe renal impairment' be included as missing information. Risk-minimisation and pharmacovigilance activities should be

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	urine radioactivity. Because the percentage of dose excreted in urine is so small (and the amount as parent ponatinib even lower), the sponsor believes that renal function is expected to show little influence on the pharmacokinetics of parent ponatinib exposure. It is acknowledged that in subjects with severe renal impairment, alterations in ponatinib exposure cannot be excluded, as circulating uremic toxins may theoretically affect plasma protein bound and hepatically eliminated drugs such as ponatinib. For this reason, the sponsor proposes cautionary language in the product information for patients with moderate or severe renal impairment creatinine clearance (< 50 mL/min/1.73m2) or end-stage renal disease. The sponsor believes that no additional warnings or precautions are required. Based on these results, the sponsor also does not believe that additional studies in subjects with renal impairment are warranted. Because the likelihood of risk is low, the risk is minimized by the product information, and no studies are planned, the sponsor does not believe that patients with renal impairment should be included in the EU RMP as missing information.	assigned as appropriate to this missing information.
3.a) It is recommended that the sponsor provides an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia	The list of studies included in the ASA to the EU RMP was not intended to repeat the list of studies included the EU RMP. The studies included in the ASA were selected based on studies that had participating sites in Australia. To address the request for an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia, the sponsor proposes not to include this list as an attachment to the ASA, but to rather refer to the EU RMP. Specifically, please refer to Part III, section 5.1 of EU RMP	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	version 9.0 that includes a table of ongoing and planned additional pharmacovigilance studies in the pharmacovigilance plan, and Section 5.2 for a table of completed studies/activities in the pharmacovigilance plan. Anticipated completion dates are also provided here. The sponsor proposes to submit the results of studies to TGA as part of PSURs or EU RMP updates. RMP evaluator's comments: The quoted text is an extract of the s31 response provided by the sponsor. For full details please refer to s31 response document.	
3.b) The sponsor addresses the missing information of 'use of ponatinib in the treatment of patients with newly diagnosed CML' by a 'Phase 3 clinical trial evaluating ponatinib versus imatinib in the treatment of patients with newly diagnosed CML. It appears that the sponsor refers to the EPIC trial which has been terminated in October 2013. Therefore, it is considered that the already gathered patient data may not be sufficient to comprehensively address this missing information. It is recommended that the sponsor comments on whether it is anticipated that this missing information can be comprehensively addressed after the EPIC trial has been discontinued. Depending on the sponsor's response it may be necessary to update this table to reflect the situation after the discontinuation of the EPIC trial.	The sponsor agrees with TGA that the data from the prematurely terminated EPIC trial do not sufficiently address the missing information of use of ponatinib in newly diagnosed patients. This situation will be updated in the EU RMP (subsequent to version 9.0) upon the update subsequent to submission of the EPIC clinical study report to EMA.	The sponsor's commitment to resolve this situation an updated RMP is considered acceptable.
3.c) It is recommended that the sponsor add the following sentence to the paragraph 'routine pharmacovigilance system in Australia' in the ASA: Activities are carried out according to the TGA	The sponsor agrees to add to the ASA the sentence: Activities are carried out according to the TGA guidelines 'Australian requirements and recommendations for pharmacovigilance	The sponsor's commitment to implement the RMP evaluator's request in an updated ASA is considered

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
guidelines 'Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines', version 1.1, dated Dec-2012 (see section 8.2).	responsibilities of sponsors of medicines', version 1.2, dated 8 August 2013 (see section 8.2).	acceptable.
3.d) The sponsor describes in this table that additional activities are conducted for Ischemic cardiac events, Ischemic cerebrovascular events and Ischemic peripheral vascular events. However, the activities listed are additional risk minimisation activities, not additional pharmacovigilance activities. Consequently, these activities should be deleted from this table in an updated version of the ASA (see section 8.2).	The sponsor regrets the oversight and agrees to delete the additional risk minimization activities from the table of pharmacovigilance activities in next update to the ASA. These activities have also been deleted from the corresponding table of the EU RMP version 9.0.	This is considered acceptable.
3.e) The sponsor describes that the potential risk of teratogenicity is addressed by an additional pharmacovigilance study. This study is an 'in vivo interaction study of the effect of ponatinib on oral contraceptives'. It appears that this study will evaluate the interaction of ponatinib and oral contraceptives and therefore, does not provide any information on the teratogenic potential of ponatinib. Consequently, it is recommended that this table be amended and reference of this study be removed from the potential risk of 'teratogenicity'. In addition, the sponsor should add 'Interaction of ponatinib with oral contraceptives' as missing information in the table of ongoing safety concerns, and assign the study to this missing information (see section 8.2).	The sponsor acknowledges the error and will remove reference to this study from the potential risk of teratogenicity in the next update to the ASA.	The sponsor's commitment to implement the RMP evaluator's request in an updated RMP is considered acceptable. Please also refer to point 2.9 in this table.
3.f) It is recommended that the	All international research efforts	The sponsor's

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
sponsor implements a registry which includes all patients in Australia receiving ICLUSIG. The information to be collected should allow evaluating important safety related points, including but not limited to: a.) Further establish the pattern of SAEs, b.) Evaluation of dose-effect and dose-toxicity relationships, c.) Development of guidelines for the management of SAEs related to ICLUSIG. The sponsor should provide all relevant details regarding a registry in their s31 response which will be evaluated by the Office of Product Review. Results of the registry should be reported to the TGA on a three-monthly basis, and reported separately in any future PSUR.	to collect data on the effects of dose, cardiovascular risk factors, and medical management of conditions that contribute to cardiovascular risk on the occurrence of vascular occlusion are expected to provide relatively robust information on the nature of the events and the possibility of mitigating their risk. These efforts include the prospectively defined trials outlined at the beginning of this response: AP24534-14-203: A Randomized, Open-label, Phase 2 Trial of Ponatinib in Patients with Resistant Chronic Phase Myeloid Leukemia to Characterize the Efficacy and Safety of a Range of Doses AP24534-14-401: A Post-marketing Observational Cohort Study to Evaluate the Incidence of and Risk Factors for Vascular Occlusive Events Associated with Iclusig® in Standard Clinical Practice in the US (Study Number AP24534-14-401). In addition to these clinical trials, several nonclinical studies have been designed and proposed to elucidate the mechanism of thrombosis associated with ponatinib (EU RMP version 9.0). The data from these trials and studies will also be applicable to the Australian population and will be reported regularly to TGA through PSURs. Because these trials are prospectively designed with requirements for rich data collection, they are expected to yield valuable additional information on the nature of vascular occlusion with ponatinib, the relative contribution of risk factors, and the value of various mitigation strategies (such as dose adjustments and prophylactic medications). As such we believe that they are directly responsive to the request to further establish the pattern of SAEs, evaluate a dose-effect and dose-toxicity relationships, and develop of	response has been noted. However, study AAP24534-14-401 collects safety data in Standard Clinical Practice in the US. The RMP evaluator questions whether standard clinical practice in the US is sufficiently similar to that in Australia and therefore, whether the data collected in this study is transferable to the Australian context. It is recommended that the sponsor elaborates on this issue, and if relevant differences in clinical practice between the US and Australia are identified, a registry or a prospectively defined trial should be implemented in Australia.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	guidelines for the management of SAEs related to Iclusig. On the other hand, given that ponatinib will be used in Australia to treat a subset of an orphan population, the few patients expected to be receiving ponatinib in Australia, and the challenge of obtaining robust data from registries in general, a registry would appear to be of limited value in providing additional information on the risks of ponatinib, particularly vascular occlusion. For example, in Response to PRAC List of Outstanding Issues (June 2014) Question 5, the sponsor undertakes an exercise in showing the sample size required to show a risk reduction in patients receiving given prophylactic measures versus those who are not (on the order of 3000 patients). The sample size is not achievable in any case, and certainly not in Australia. The sponsor believes that the best course in evaluating the nature of the risks and the most successful strategies for mitigating them is through prospective studies and aggregated reports (such as the PSUR) that will allow comparison across larger populations. Finally, it should be noted that in the final version of the REMS agreed with US FDA, no registry is being implemented. The sponsor and FDA agreed that the most appropriate REMS is one that focuses on the communication of the risks of Iclusig (see www.iclusigrems.com). The REMS now consists primarily of a communication program that is similar to that being implemented in Europe. The European model will serve as a template for the educational program in Australia.	
4.) In section 3.3 of the ASA (Details of additional risk minimisation activities, by	The EU RMP version 6.0 included additional risk minimization activities of a direct healthcare	The sponsor's response has been noted. However,

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Safety Concern) the description of the additional risk minimisation activities differs from the description provided in the EU-RMP. The ASA should be revised to correct this inconsistency in the document (see section 10.1).	professional letter (DHCP), a brochure for healthcare professionals, and a brochure and alert card that are aimed toward patients. PRAC did not endorse the patient-focused materials, and so they have been removed from the latest version of the EU RMP (version 9.0). The inconsistency between the proposed risk minimization activities in the EU RMP and the ASA was as a result of ongoing discussions in the EU to change the proposed risk minimization activities as was stipulated in EU RMP version 6.0. The ASA at the time anticipated the changes, and EU RMP version 9.0 reflects the current risk minimization activities based on PRAC comments. With the update of the EU RMP, the ASA will then be aligned with the EU RMP in terms of proposed risk minimization activities. At the time of submission of the ASA v2.0 the sponsor neglected to clarify that the preliminary feedback from the PRAC indicated that the patient educational materials are not endorsed. ARIAD acknowledges that this discrepancy between the ASA and the EU RMP was significant, but insufficiently explained in ASA v2.0. Please also see Response to TGA RMP Request 5.	implementation of a patient card is recommended (see following point 5 in table 5 below).
5.) It is recommended the ASA be amended to include the implementation of a patient educational program in Australia, as it is proposed for Europe. Furthermore, there is no mentioning of a patient card in the ASA. This is considered unacceptable, and the ASA should be revised to include this additional risk minimisation activity in Australia.	The use of a patient educational program and patient card was ultimately not supported by PRAC, and so this proposal has been retracted, as reflected by EU RMP version 9.0. Because Iclusig will be prescribed by specialists who are closely involved in their patients' care, it was felt that the primary responsibility for informing patients of the risks should fall to their physicians, and therefore, the greatest benefit of educational programs would be those directed at healthcare professionals.	The response has been noted. However, the RMP evaluator is of the opinion that implementation of a patient card will be beneficial to ensure that: A.) Patients are informed about the risk of cardiovascular events, B.) Patients are aware of any symptoms relating to cardiovascular

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	Therefore, in the EU, the sponsor has retained the direct healthcare professional communication (DHPC) and healthcare professional brochure. The ASA is therefore consistent with the risk minimization activities currently endorsed in EU.	events, C.) Patients will be able to communicate that they do receive ICLUSIG, and the risk of cardiovascular events to any HCP that may be involved in the patients care other than their haematologist / oncologist. Consequently, implementation of a patient card is recommended.
6.) It is recommended that the following sentence, located in section 3.3 of the ASA, be changed to the sentence shown in bold writing: Future changes will be considered and, if feasible and applicable to the Australian environment, the additional risk minimization activities in Australia will be closely aligned with that of the EU. Future changes will be implemented in Australia, unless there are compelling reasons for not doing so, and the additional risk minimisation activities in Australia will be closely aligned with that of the EU (see section 10.1).	The sponsor agrees to this change. The change will be applied to the next update of the ASA.	This is considered acceptable. The updated ASA will be reviewed once received.
7.a) The sponsor states: HCP educational material will be available at the time of launch of Iclusig. These will be distributed to healthcare professionals for the first 2 years from launch of ICLUSIG in Australia. It is recommended that the length of distribution will be determined depending of the data obtained by effectiveness measures (please see below). It is recommended the wording to be changed to: HCP educational material will be	The sponsor agrees to the suggested change, with the following amendment: HCP educational material will be available at the time of launch of Iclusig. These will be distributed to HCPs for at least two 2 years from launch of Iclusig in Australia. Distribution of documents will be ceased after the initial two year period if the results of the effectiveness measures indicate satisfactory education of HCPs about existing safety risks and management of side effects, or if	This is considered acceptable. The updated ASA will be reviewed once received.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
available at the time of launch of Iclusig. These will be distributed to healthcare professionals for at least two 2 years from launch of Iclusig in Australia. Distribution of documents will be ceased after the initial two year period if the results of the effectiveness measures indicate satisfactory education of HCPs and patients about existing safety risks and management of side effects.	otherwise agreed with the TGA. Please see the ARIAD Response to TGA RMP Request 5: the educational materials comprise HCP educational materials that provide further details about the risks of Iclusig.	
7.b) The sponsor states: In order to evaluate the extent of the brochures and alert cards distribution, ARIAD will work with a market research tool to develop a survey aiming at assessing the awareness of the HCP educational material and the level of knowledge achieved by the risk minimization measures. Furthermore, the sponsor states: Assessment of these measures is foreseen at 18 and 30 months following launch. It is considered that the timeframes for evaluation of the effectiveness of the additional risk minimisation activities after 18 and 30 month is not acceptable. It is recommended that the sponsor conducts the first evaluation of assessment after an initial 6 month period. The results of the evaluation of effectiveness should be reported in any PSUR[52]. Furthermore, the sponsor should amend the ASA to describe the criteria which will be used to determine success or failure of the additional activities. These criteria will be evaluated by the TGA.	In the EU RMP version 9.0, the evaluation plan has been updated to assess the measures at 12 and 24 months after initial distribution of the HCP letter. Further details will be available with the update of the EU RMP subsequent to version 9.0, reflecting additional development of the plan. In Australia, considering that the indicated population represents an orphan disease, it is not believed that sufficient data will be available 6 months after product launch. Therefore, in Australia, the sponsor proposes to follow the evaluation plan put forth in the EU RMP. The results of the evaluation of risk minimization activities will be reported in the applicable PSURs and in updates to the EU RMP. Details of the evaluation plan in Australia are still being developed. If the evaluation plan in Australia will be performed independently from the global plan, the results will be provided as an annex to the PSUR at the time of the submission of the PSUR to the TGA, and included in the ASA to the EU RMP.	This is considered acceptable.
8) The following recommendations are made	The content of the Healthcare Professional Educational material	This is considered acceptable. The

[52] PSUR=Periodic Safety Update Report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
regarding the educational programs for HCPs and patients and regarding the patient card. 8.a) It is recommended a 'boxed warning' be included on the first page of the patients and HCPs and brochure to inform the audience about the recently observed safety issues, and to outline more strongly the underlying reasons for providing these brochures to the target audience.	is being developed. It will contain, at a minimum, the same content as is being proposed in Europe. Please see EU RMP Version 9 Annex 11 for a copy of the latest proposed Healthcare Professional Brochure. The sponsor proposes to await the outcome of the discussions on the need for a boxed warning in the Australian Product Information. The sponsor will align the HCP educational materials with the Product Information.	commitment to include a boxed type warning in the HCP's materials, if the Delegate requires a boxed warning in the Australian PI, has been noted.
8.b) The dimensions of the patient card appear to be too big to be carried by the patient. It is recommended that the sponsor re-designs the patient card to be smaller so it can be carried by the patient at all times. It is recommended that the sponsor comments on the dimensions of the patient card and re-designs the card to decrease the size so it can be carried in the patient's wallet at all times.	Because no patient materials are planned for any region at this time, this is no longer applicable.	This recommendation remains (see also point 5 in this table).
8.c) It is recommended that the patient card and the patient brochure will be attached to each other and presented as one document. This will ensure that all important information will be communicated to the patient at the time of first prescription.	Because no patient materials are planned for any region at this time, this is no longer applicable.	As the sponsor does not propose to implement a patient brochure, this point is not applicable anymore. However, the RMP evaluator believes that the patient card should be implemented (see point 5 in table5).
8.d) It is recommended that the sponsor clarifies how distribution of these documents will be carried out, and comments on the HCP group which will be a target of the HCP brochure distribution. It is considered important that nurses and pharmacists also be comprehensively educated about the safety issues. The	The sponsor is currently distributing a document named 'Important Safety Information Regarding Iclusig' to all prescribers who request Iclusig for the treatment of their patients via the Special Access Scheme (see Appendix 1). This document is based on the Direct Healthcare Professional Communication that was distributed in the EU (2	It is understood that the sponsor believes that it will be sufficient to educate specialised physicians and HCPs only about the potential risk of cardiovascular events associated with Iclusig.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
sponsor should comment on whether this brochure will be distributed to prescribers only, or whether this brochure will also be distributed to other HCPs including nurses and pharmacists, and how distribution to other HCP groups will be controlled.	December 2013), and will be revised continuously to keep it aligned with the HCP educational content in Europe and the approved Australian PI. At the time of Iclusig launch, controlled supply on a named patient basis will no longer be possible. Iclusig will however be prescribed by a relatively small number of specialist physicians experienced in the treatment of the target disease, and due to the refractory nature of the treated population, it is expected that these patients will be intensively monitored by their treating physicians, and it is highly unlikely their routine care will be referred to their general practitioner. Pharmacists and nurses outside of haematology and oncology units will have limited interactions with these patients, and all educational sessions to pharmacists and nurses will be focused on the personnel working at specialty hospitals and clinics only. Therefore, the sponsor proposes the following distribution plan in order to ensure initial and continued awareness of important safety issues associated with Iclusig. The exact format of the information is yet to be confirmed, but the sponsor can affirm that the content will include as a minimum all the information that are included in the HCP educational brochures that will be distributed in the EU. At launch: 1) Distribution of the educational materials (both electronically and as hard-copies) to all potential prescribers of Iclusig. This will include approximately 400 specialist haematologists, haematologists/oncologists and haematology registrars (Note: It should be recognized that given the small patient population and	However, the RMP evaluator believes that HCPs other than their prescribing haematologist/oncol ogist may be involved in a patient's ongoing care. Therefore, it is considered important that some mechanisms exist which will allow informing any HCP, who may be involved in a patient's care, about a patient taking Iclusig and about the potential cardiovascular risks associated with it. One such mechanism could be the patient alert card, which the patient can present to any HCP during a consultation (see point 5 in this table).

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	therefore a relatively discrete number of specialists/haematologists managing these patients, the sponsor will provide additional focus on liaising with the CML and Ph+ALL treating physicians). 2) Communication/distribution of the educational materials to all relevant heads of departments at major haematology hospitals 3) Communication/distribution of the educational materials to all presidents of relevant professional organisations in this field. After launch: 1) Face-to-face visits by STA[53] representatives to all prescribers to specifically discuss and distribute the safety educational materials. Visits will be prioritised according to anticipated/actual uptake of Iclusig and also further targeted at the CML and Ph+ ALL treating physicians. The target is to meet all actual prescribers face-to-face as soon as possible, but no later than within the first year after launch. 2) In-service visits by STA representatives to nurses and pharmacists at major haematological centres to specifically discuss and distribute the safety educational materials. Visits will be prioritised according to uptake of Iclusig.	
8.e) It is recommended that that a 'safety information document' be distributed to all relevant professional organisations in Australia. This will ensure that all health care professionals, involved in the management of patients using Iclusig, are comprehensively informed about safety related information relevant for the	The sponsor agrees with the recommendation to distribute a 'safety information document' to all relevant professional organisations in Australia. The sponsor has identified the following three relevant organisations: Haematology Society of Australia & New Zealand (HSANZ), the Haematology Association of	This is considered acceptable at this time.

[53] STA=Specialised Therapeutics Australia

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
product.	Australasia (HAA) and the Australasian Leukemia and Lymphoma Group (ALLG). As per response to question 8D, information will be sent to the presidents of these societies at the time of launch, as part of the overall communication plan – with the intention of further dissemination of this information across the organisation's membership.	
9.) Recommendations to the PI and CMI. 9.1) Underlining Non-haematological adverse reactions, Vascular occlusion, and Pancreatitis	ARIAD agrees to make these formatting changes in the updated PI.	Pending the Delegate's approval, this is considered acceptable.
9.2) It is recommended that the 'Precautions' section of the PI makes reference to the healthcare professional educational materials regarding vascular occlusion events	ARIAD proposes not to include reference to the healthcare professional materials in the PI. The content of the HCP materials will be closely aligned with information in the PI – including, where known, information on the risks, pre-treatment advice, monitoring advice and contra-indications. The information in the PI will be comprehensive enough not to require reference to another document. Furthermore, the distribution of the additional educational material is anticipated to be a temporary measure to ensure awareness of these risks during a time when experience with the product is relatively limited and the risks associated with the product are still relatively unknown. Cessation of or changes to this activity in the future would mandate changes to the PI. Whilst the HCP materials will be a valuable tool in raising awareness about the risk associated with the product, prescribers should refer to the PI in the first instance as the reference document for Iclusig.	This is considered acceptable at this time.
9.3) Changing the dosing recommendations in the PI	ARIAD agrees.	Pending the Delegate's approval,

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
consistent with the FDA-REMS[54]		this is considered acceptable.

Summary of recommendations

It is considered that the sponsor's response to the TGA's request for further information has not adequately addressed all of the issues identified in the RMP evaluation report (see 1. Outstanding issues below)

Outstanding issues

Issues in relation to the RMP

1. No ASA was provided in the sponsor's response and therefore, all statements/recommendations made in this report are based on the sponsors response and EU-RMP version 9.0. The appropriateness of risk minimisation and pharmacovigilance activities in the Australian context will be evaluated once the updated ASA has been received.
2. It is recommended that the updated ASA be submitted as soon as possible , at the latest at the sponsor's Pre Advisory Committee on Prescription Medicines (ACPM) response, so the ASA can be evaluated and necessary changes to the document be negotiated.
3. It is recommended to the Delegate to draw the attention of the nonclinical evaluator to assess the appropriateness of the sponsor's justification to remove the missing information of 'plasma exposure to metabolites' (see point 2 in Table 19 above).
4. The RMP evaluator maintains the position, that '*Ponatinib treatment during pregnancy and in breast-feeding women*' should be added as missing information to the table of ongoing safety concerns in an updated RMP/ASA. Appropriate pharmacovigilance activities to monitor this missing information should be implemented (see point 2.10 in Table 19above).
5. As risks to the safety of patients with severe renal impairment cannot be excluded, it is recommended that '*safety in patients with severe renal impairment'* be included as missing information. Risk-minimisation and pharmacovigilance activities should be assigned as appropriate to this missing information (see point 2.11 in Table 19 above).
6. The RMP evaluator is of the opinion that implementation of a patient card will be beneficial to ensure that:
    a. Patients are informed about the risk of cardiovascular events
    b. Patients are aware of any symptoms relating to cardiovascular events
    c. Patients will be able to communicate that they receive Iclusig and the risk of cardiovascular events to any Health care professional (HCP) that may be involved in the patients care other than their haematologist/oncologist.

    Consequently, implementation of a patient card is recommended.
7. Study AAP24534-14-401 collects safety data in Standard Clinical Practice in the US. The RMP evaluator questions whether standard clinical practice in the US is sufficiently similar to that in Australia and therefore, whether the data collected in

[54] REMS= Risk Evaluation and Mitigation Strategy

this study is transferable to the Australian context. It is recommended that the sponsor elaborates on this issue, and if relevant differences in clinical practice between the US and Australia are identified, a registry or a prospectively defined trial should be implemented in Australia.

8. Study protocols/synopsis for studies referenced in point 3.7f in table above, and referenced throughout the RMP, should be attached as Annex to the RMP.

9. The Advisory Committee on the Safety of Medicines (ACSOM) noted that at the time of the first round RMP evaluation inconsistencies existed, in terms of the numbers provided relating to the occurrence of arterial thrombotic events, between the Australian PI, the HCP educational materials, the EU Summary of Product Characteristics (SmPC) and the US PI. It is recommended that the sponsor ensures that the numbers which are provided in the Australian PI are consistent with numbers in the HCP brochure, the US PI and the SmPC.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

The ratified ACSOM advice for ponatinib is shown below:

1. Can the committee comment on the completeness of ongoing safety concerns listed in the table of ongoing safety concerns in the RMP?

In reviewing the safety concerns, the committee noted that the length of exposure to ponatinib did not extend beyond 24 months in most studies and that the assessment of the ongoing safety concerns was limited by the termination of the phase three EPIC trial. However it was noted that comparisons can be made with other tyrosine kinase inhibitors, such that class effects can be anticipated.

ACSOM noted that the cumulative number of treatment-emergent arterial thrombotic and venous occlusive events observed earlier in development have increased with an additional 13 months of follow-up since data cut-off for the application. Non-serious arterial and venous adverse events occurred in at least 20% of ponatinib treated patients and the EPIC trial was discontinued due to an increase in cardiovascular events in the ponatinib arm.

The committee discussed the data from the PACE trial including the Phase I and Phase II studies, and noted that 530 patients in the safety population were exposed to ponatinib as a second line therapy with an equivalence of almost 428.81 patient–years; the majority of patients were older than 65 years and had co-morbidities. Most patients were exposed to a 45 mg dose and there were no paediatric patients.

The committee advised that the list of ongoing safety concerns in the Risk Management Plan (RMP) is incomplete and that it should be updated in line with the RMP evaluator's recommendations. ACSOM agreed with the RMP evaluator that the following safety concerns currently listed as *potential risks* have sufficient evidence available to be moved to the *identified risks* in the table of ongoing safety concerns:

- QT-prolongation, arrhythmias (tachycardia, atrial fibrillation)
- retinal vascular events
- hypertension be included as high blood pressure
- bleeding
- hypophosphatemia and related symptoms
- peripheral neuropathy events
- cranial neuropathy events
- thyroid function disorder.

ACSOM noted and agreed with the RMP evaluator that the following be included as *missing information* in the RMP:

- plasma exposure to metabolites
- pregnant and breast feeding women and risks to neonates
- interaction of ponatinib with oral contraceptives
- patients with renal impairment.

2. *Can the committee please comment on the appropriateness of the proposed risk-minimisation activities (Patient educational materials, Health Care Professional educational materials, Patient Card). Furthermore, does the committee agree that risk minimisation activities in Australia should be closely aligned to the activities mandated by the FDA-REMS?*

ACSOM noted that there were a number of inconsistencies in the materials provided regarding the risk minimisation activities which are planned for implementation in Australia. For example, the education programme for patients in Europe does not appear to be proposed for implementation in Australia. The committee advised that in order to be able to adequately assess the appropriateness of the proposed activities, it is important that the sponsor provide more definitive statements regarding the activities that will be implemented in Australia.

ACSOM advised that patient and health professional educational materials and a patient alert card, would be adequate activities, however it would be important to ensure that they are comprehensive and consistent and that the RMP and Australian Specific Annex be updated and cross referenced.

In assessing the content/details of the proposed materials, ACSOM noted that there were inconsistencies between the reported figures for arterial and venous thrombosis and occlusions, on the fact sheet, in the letter for health care providers and in the background material reported to the TGA in September 2013. The EMA physician information referred to serious arterial thrombosis (12 % of patients) whereas the US black box warning and fact sheet (FDA) has all arterial thrombosis events (approximately 20%). It was advised that although these materials are appropriate, consistency is required.

It was noted that access to a website is also available however the information provided on the web site is relevant to the US context (Dear HCP letter/FDA safety communication/ARIAD pass/Iclusig REMS and updates/Important safety information/Prescribing information/Medication guide). It was not clear whether there are plans to develop this website for use in the Australian context.

ACSOM further advised that risk minimisation activities need to be appropriate for people living in rural and remote regions of Australia; in these regions there is less access to health services than in an urban setting and online information may not be as accessible to patients. The committee noted that it is crucial that to mitigate risk in this population, patients need to have easy access to current information.

The committee also advised that despite journal notices being used as a forum for communication, that the trend for the use of electronic delivery may reduce exposure to readers for these notices. Instead it was advised that a letter to professional societies in Australia may be a more appropriate communication tool.

In addition, the ACSOM noted that the sponsor proposed to assess the effectiveness of the health professional education at 18 and 30 months following the launch. The committee advised that this was not appropriate and that consideration be given to evaluating the effectiveness at earlier time intervals post-launch.

With respect to aligning the Australian activities with those mandated by the FDA-REMS, ACSOM advised that in order to ensure best practice and consistency in the collation and contribution of information about ponatinib it would be appropriate to align the risk minimisation activities in Australia with those mandated by the FDA.

3. *Since the EPIC trial (Phase III trial) has been discontinued and no safety data will be collected in a Phase III trial, does the committee agree there is a need to collect further safety related data in Australia? If so, does the committee consider a registry to be the most appropriate method of data collection, or can the committee advise on a suitable alternate data collection methodology?*

ACSOM recognised that ponatinib is being used in people with a lethal condition but there remains a need to identify ways to monitor the risk of common arterial events and venous thrombotic events and more information about the mechanism of action of these events is required.

The committee agreed that following the discontinuation of the EPIC trial, there is an explicit need to collect further safety related data for ponatinib in Australia. ACSOM noted that ponatinib is likely to be used long term, however there is limited data on use beyond 24 months. ACSOM also noted that the adverse events following treatment with ponatinib are not immediate and they tend to occur after a period of treatment. It is therefore necessary to ensure that follow up data collection occurs for patients in the trial to ensure that the adverse events are captured. The committee advised that further safety data is required to recognise the underlying cause and mechanism of action of adverse events so that it might be possible to identify patients at higher risk of developing these events.

It was noted that patients provide useful information which can be used to determine rates of adverse events and ACSOM favours the collection of data early followed by more detailed clinical studies to further assess the mechanism of action. ACSOM agreed that ongoing pharmacovigilance activities are required and discussed the advantages and limitations of using a registry to support data collection. Reliance on health professionals reporting adverse events, despite encouragement, can be problematic; registries require data reporting and entry and the infrastructure may not be widely available. It was further noted that registries are only as good as the data that is entered.

ACSOM advised that a possible alternative method of data collection was to link a patient's access to ponatinib to the reporting of adverse events; this could provide an effective way of ensuring adverse events are reported. Such an activity would need to be supplemented by ongoing trials which would specifically address the long term use of ponatinib. The committee advised that as data collected will be reported in the Periodic Safety Update Reports (PSURs) that more frequent analysis of the PSURs could provide early information.

Additional advice

The committee considered the issue of dosing for ponatinib. It was noted that the dose is important in achieving major treatment milestones, which leads to improved long term survival. It was unclear to ACSOM what the justification of the dose was and why the dosing for patients' treatment began at 45mg and then had the dose reduced to manage adverse events, rather than beginning with 30mg in the first instance. In light of this, ACSOM advised that the Delegate may wish to consider the evidence to support the proposed starting dose.

Key changes to the updated RMP

In their response to the TGA's request for further information the sponsor provided an updated RMP (version 9.0, dated 4 June 2014). Various changes to the safety specification were made as compared to the previously evaluated RMP version 6.0.

Suggested wording for conditions of registration

RMP

The EU-RMP, version 9.0, dated 4 June 2014, data lock point 6 January 2014, with Australian Specific Annex (subsequent to version 2.0), to be revised to the satisfaction of the TGA, must be implemented.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are stability issues with the tablets and a shelf life cannot yet be recommended. Stability is likely to be better with bottle packs containing a desiccant, which are currently being investigated by ARIAD. Updated details should be available at the time of the ACPM meeting.[55]

Registration is otherwise recommended with respect to quality and biopharmaceutic aspects.

Nonclinical

The nonclinical evaluator noted the overall quality of the dossier was high and recommended that with monitoring and management of the observed toxicities there were no objections on nonclinical grounds to registration of ponatinib.

The primary pharmacology studies generally support the proposed use of ponatinib as an oral agent for the treatment of patients with CML or Ph+ ALL that is resistant to imatinib, dasatinib or nilotinib, though efficacy will be somewhat dependent on the BCR-ABL mutation present.

The combined animal safety studies revealed the following findings of potential clinical relevance:

- Heart murmurs
- Pancreatic damage and pancreatitis
- Immunosuppression and risks for infection
- Anaemia
- Haemorrhages and bleeding episodes
- Changes in thyroid hormones and thyroid effects
- Skin lesions
- Photo-ocular damage

Provided the above effects are adequately monitored and manageable from a clinical perspective, there were no objections on nonclinical grounds to the proposed registration of Iclusig.

See Nonclinical summary and conclusions above.

[55] Data was subsequently submitted which supported the 18 month shelf life when stored below 30ºC.

Clinical

Following the concerns raised by the FDA regarding vascular adverse events, the sponsor submitted an addendum to the Clinical Overview, which included additional safety data and this was evaluated in the first round clinical evaluation report.

In the second round of clinical evaluation, the sponsor's responses to the clinical evaluator's questions (including the request for the Phase III trial safety data) and also the questions raised by the EMA and the sponsor's responses to these were also evaluated. These are discussed in the Second Round section of the CER.

The submitted data was evaluated using TGA adopted EU Guidelines as follows:

- Guideline on the evaluation of anticancer medicinal products in man
- Appendix 4 to the guideline on anticancer medicinal agents, which is concerned with trials in haematological malignancies.

Clinical evaluator's recommendation

The clinical evaluator recommended that the application for the registration of ponatinib be approved.

Summary of PK data

No clinical data were included in the submission to define the sites and mechanisms of absorption. The T_{max} for ponatinib at steady state at the recommended dose of 45 mg daily was approximately 5 hours. The C_{max} and AUC increase in a dose proportional manner, with accumulation demonstrated with multiple dosing in patients with advanced haematological malignancies taking 15-45mg daily (ratio 1.74 to 2.17). Food did not have an effect on levels but the quality evaluator noted that the drug has low solubility in anything other than strong acid and potentially decreased absorption where the gastric pH is raised: achlorhydria/age, concomitant use of medications that raise the including antacids, H2-receptor antagonists and proton pump inhibitors. The sponsor provided a description of Study 108 but no study report, in the updated submission examining the effect of lansoprazole on the PK of ponatinib. There did not appear to be a significant decrease in ponatinib AUC (6 to 8%) but this study should be submitted for evaluation as a Category 1 application (See *Conditions of Registration*).

There was no study of absolute bioavailability. This means the systemic absorption is determined indirectly from the mass balance studies and the degree of biotransformation (65%) but important PK parameters such as clearance and volume of distribution cannot be determined. This does not meet the requirements of the guidelines for data required for new chemical entities.

The volume of distribution of 926 to 1410 L determined from steady state in patients being treated suggests wide tissue distribution, without any clinical data form tissues to clarify this further.

Clearance is predominantly hepatic with 5% of the oral dose was excreted in the urine with <1% unchanged (estimated from the mass balance study). This is presumed to be hepatic clearance although no data were submitted. There appear to be numerous pathways for metabolism, with in vitro data indicating metabolism by CPY3A4.

Initially a capsule formulation was used in the Phase I study, then a tablet formulation thereafter with C_{max} and AUC similar between them but no formal bioequivalence was established for either.

> **Delegate comment**: There are deficiencies which raise uncertainties about the metabolism, volume of distribution (Vd) and clearance (CL) of ponatinib. It is unclear

whether the accumulation seen with repeat dosing is contributing to the increase in adverse events seen in these subjects. However, it is noted that dose reductions below 45 mg led to a loss of response in such patients.

There appear to be no clinically active metabolites and 25% of the circulating ponatinib was unchanged. Excretion was predominantly in the faeces.

There was up to 50% inter-subject variability of both C_{max} and AUC at the 45 mg/day dose.

Delegate comment: The sponsor is requested to comment as to why such variability occurs (see *Questions for sponsor*).

Pharmacokinetics of special populations

Ponatinib clearance appears to decline with age.

Hepatic impairment

A study in those with hepatic impairment (Child Pugh Classes A, B C)[56] compared with matched controls with normal liver function demonstrated that the ponatinib elimination half-life was increased in subjects with hepatic impairment but with no discernible pattern of increasing ponatinib exposure with increasing levels of hepatic impairment. The sponsor concluded that the data did not indicate a need for dosage reduction in subjects with hepatic impairment and the clinical evaluator and Delegate are in agreement with this. It is noted the population PK study that examined the effect of AST, ALT and bilirubin levels on ponatinib PK did not include patients with significant dysfunction.

Renal impairment

There were no studies examining the effect of renal impairment on ponatinib but as renal excretion did not appear to be significant, this is acceptable.

PK interactions

Co-administration of ponatinib with the CYP3A4 inhibitor ketoconazole had a significant effect on systemic exposure to ponatinib, with AUC_{∞} increasing by 78% and C_{max} increasing by 47%. Study 107 (described but not submitted for evaluation in the second round evaluation phase) indicates co-administration of rifampicin resulted in a reduction in ponatinib AUC of approximately 60% and a reduction in ponatinib C_{max} of 42%. This is clinically relevant and informs prescribers so should be included in the PI now and the study submitted for evaluation as a Category 1 submission (see *Conditions of Registration*). This, together with the potential for reduced absorption with drugs increasing the gastric pH were the only significant drug interactions and these have both been communicated adequately in the PI.

Pharmacodynamic effects

In Study 101, the levels of pCRKL[57] (a surrogate for BCR-ABL activity) were reduced by ponatinib, consistent with inhibition of BCR-ABL activity. The clinical relevance of this biomarker is not established.

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[56] The Child-Pugh score is used to assess the prognosis of chronic liver disease, mainly cirrhosis. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement (see tables below).

Points	Class	One year survival	Two year survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Measure	1 point	2 points	3 points
Total bilirubin, µmol/l (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
PT INR	<1.7	1.71-2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

[57] Phosphor-Crk-like protein is a protein that in humans is encoded by the CRKL gene (v-crk avian sarcoma virus CT10 oncogene homolog-like)

Dose selection

A 45 mg dose was the MTD in the first in human study (Study 101). Dose-limiting toxicities in decreasing order were pancreatitis (4), fatigue (1) and elevated liver enzymes (1).

> **Delegate comment**: The percentage of subjects requiring dose reductions in subsequent studies suggests that the MTD was not adequately established.

Efficacy

Study 201 was a Phase II, single arm, open label trial multicentre (68 centres in Australia, Europe, Asia and the North America) in patients with CML or Ph+ ALL. Patients were enrolled into cohorts depending upon their disease stage and the presence of the T315I mutation.

Primary objectives: to determine efficacy of ponatinib in patients with CML in CP, AP, or BP or with Ph+ ALL who were either a) resistant or intolerant to either dasatinib or nilotinib or b) had the T315I mutation.

Secondary objectives: to 1) further characterise the anti-leukemic activity of ponatinib in these patients (clinical responses, molecular responses, and clinical outcomes) 2) characterise the molecular genetic status of patients; and 3) examine the safety of ponatinib in these patients.

The stages of CML are shown in Table 20. Inclusion and exclusion criteria were summarised. Those with a T315I mutation need not necessarily have had prior dasatinib or nilotinib. Data for any subject with a prior history of a positive T315I mutation subsequently found to have a negative mutation test after enrolment was not included in the efficacy analyses.

Table 20: Study 201 - Definition of CML phases

CML Phase	Criteria
Chronic Phase (CP)	<15% blasts in peripheral blood or bone marrow **and** <20% basophils in peripheral blood **and** <30% blasts + promyelocytes in peripheral blood or bone marrow **and** ≥100 x 10^9 platelets/L in peripheral blood **and** No extramedullary disease
Accelerated Phase (AP)	≥15% and <30 % blasts in peripheral blood or bone marrow **or** ≥20% basophils in peripheral blood or bone marrow **or** ≥30% blasts + promyelocytes in peripheral blood or bone marrow (but < 30% blasts) **or** <100 x 10^9 platelets/L in peripheral blood unrelated to therapy **or** Cytogenetic, genetic evidence of clonal evolution **And** No extramedullary disease
Blast Phase (BP)	≥30% blasts in peripheral blood or bone marrow **or** Extramedullary disease other than hepatosplenomegaly

All patients were commenced on 45 mg daily, taken with or without food, with the option to decrease to 30 mg or 15 mg daily if unacceptable toxicity. Treatment continued until disease progression, unacceptable toxicity or intolerance or withdrawal by either patient or physician.

The main efficacy outcomes were haematological, cytogenetic and molecular response rates.

The primary efficacy outcome for patients with chronic phase CML (Cohorts A and B) was major cytogenetic response (MCyR) rate (that is, the proportion of patients who achieved either a complete or partial cytogenetic response [CCyR or PCyR]).

The primary efficacy outcome for patients in the other cohorts (C to F) was major haematological response (MaHR) rate (that is, the proportion of patients who achieved either complete haematological response [CHR] or no evidence of leukaemia [NEL]).

Disease progression was defined as per Table 21 below. Details of the assessments and time intervals required to establish the response are summarised in the CER (Attachment 2). The statistical plan was designed according to the stage and disease under consideration.

Study 201: Definitions for disease progression

Criteria for progression:

1. Progression from CP-CML (O'Brian et al, 2003)
    a. Death
    b. Development of AP-CML or BP-CML
    c. Loss of CHR (in the absence of cytogenetic response)
    d. Confirmed by development in CBCs at least 4 weeks apart
    e. Loss of MCyR
    f. Increasing WBC in patients without CHR defined by doubling of WBC to >20K on 2 occasions at least 4 weeks apart (after the first 4 weeks of therapy)
2. Progression from AP-CML
    a. Death
    b. Development of confirmed BP-CML
    c. Loss of previous major or minor hematologic response over a 2 week period
    d. No decrease from baseline levels in percentage blasts in peripheral blood or BM on all assessments over 4 week period
3. Progression from BP-CML or PH+ALL (Talpaz et al, 2066)
    a. Death
    b. Increasing blasts in peripheral blood or BM over a 4 week period

Enrolments in the T315I mutation arms were slower and therefore, the total number accrued to the study was increased from 320 to 450 subjects. Despite the increase, the AP-CML T315I only accrued 18 of the planned 40 subjects. The clinical evaluator noted a protocol violation in 16.5% of AP-CML patients who already had a MaHR at baseline and were analysed as non-responders may have led to an underestimation of efficacy in an already underpowered group.

This was a heavily pre-treated population (449 subjects) the median number of 3 previous TKIs (range 1-5). A total of 58.4% of the population had used 3 or more TKIs. Imatinib had been used by 95.8% of the population, dasatinib by 83.5% and nilotinib by 65.5%. The proportion of subjects who had used all three of the approved TKIs (imatinib and dasatinib and nilotinib) was 52.8%.

A total of 151 subjects (33.6%) had received prior treatment with interferon and 22.7% had received cytarabine.

Some 55.9% had a mutation detected with the most common being T315I (28.5%) followed by F317L (8.0%), E255K (4.0%) and F359V (3.8%).

Results

At the time of the July 2012 data cut-off, 252 patients (56.1% of the total) remained on therapy, and median follow-up was 9.9 months (range: 0.1 month to 18.4 months).

Chronic phase CML

For Cohort A, the MCyR rate was **48.8%** (95% CI: 41.7, 55.9%). For Cohort B the MCyR rate was **70.3%** (95% CI: 57.6, 81.1%). In both cohorts the majority of the responses were complete (CCyR) rather than partial (PCyR). Per protocol analysis was comparable.

Data were presented on CP-CML subjects who had achieved a MCyR and who subsequently had a dose reduction:

- There were 44 subjects who achieved a MCyR while taking 45 mg per day, and had a subsequent dose reduction. All 44 subjects (100%) maintained the MCyR
- There were 20 subjects who achieved a MCyR while taking 30 mg per day and had a subsequent dose reduction. A total of 18 subjects (90%) maintained the MCyR.

Delegate comment: On the basis of these data, the sponsor suggests that dose reduction in subjects who have achieved a response might reduce the risk of arterial AEs. A recommendation along these lines has been included in the US prescribing information, but does not appear in the draft Australian PI.

Accelerated phase CML

For Cohort C the MaHR rate was 60.0% (95% CI: 47.1, 72.0%). For Cohort D the MaHR rate was 50.0% (95% CI: 26.0, 74.0%). In both cohorts the majority of the responses were complete haematological responses (CHR) rather than 'no evidence of leukaemia' (NEL). Per protocol analysis gave somewhat improved results (MaHR 0f 73.6% in Cohort C and 60.0% in Cohort D), because those with a MaHR at baseline were excluded from the analysis. A sensitivity analysis was conducted on the first 40 subjects enrolled into Cohort C, and the results were comparable to those obtained with the primary analysis.

Blast phase CML / Ph+ALL

For Cohort E the MaHR rate was 35.4% (95% CI: 22.2, 50.5%). For Cohort F the MaHR rate was 32.6% (95% CI: 19.5, 48.0%). In both cohorts, the majority of the responses were again complete haematological responses (CHR) rather than 'no evidence of leukaemia' (NEL). Per protocol and sensitivity analyses gave comparable results.

Delegate comment: The response rates exceed those set as a minimum in the statistical analysis plan (which were based on having failed only a single TKI) as well as those seen with the last prior TKI treatment. Further improvements in the CML cohort could be expected with longer follow-up. These findings support ponatinib being an efficacious agent for the proposed indication.

Other efficacy outcomes

Response rates

Findings of note include:

- Over 90% of CP-CML patients achieved a complete haematological response
- MCyR were achieved in a significant proportion of patients with advanced and blast phase CML and Ph+ ALL. In particular 15/32 (46.9%) of subjects with Ph+ ALL achieved a MCyR

- Major molecular response rates were generally low (apart from those in Cohort B, where MMR rate was 50.0%). This may reflect the advanced nature of the disease as well as the short duration of follow-up.

Duration of response

The median duration of response had not been reached, indicating the high probability of maintaining a response in the chronic phase CML cohorts was high at both 6 and 12 months. For those with a T315I mutation in accelerated phase CML or blast phase CML/Ph+ ALL, the median durations of response were 5.7 months and 4.1 months, respectively. For those in the accelerated phase CML with resistant disease or intolerance of other TKIs, the median duration of response was 9.5 months.

Delegate comment: Although not randomised data, these patients have few treatment options remaining and indicate that ponatinib is an active and effective treatment in such patients.

Time to response

Among responders, the median (range) time to MCyR was 85 (56-334) days in Cohort A and 84 (49-333) days in Cohort B. The median times to complete haematological response (CHR) in these cohorts were 13 (1 to 166) and 10 (4 to 98) days respectively.

Delegate comment: This is important when considering when to make dose reductions to avoid toxicity or discontinue therapy due to lack of efficacy.

The median (range) times to MaHR in the other cohorts were:

- 21 (12-112) days in Cohort C
- 19 (14-176) days in Cohort D
- 28 (14-168) days in Cohort E
- 24 (11-57) days in Cohort F.

Progression-free survival (PFS)

For patients with chronic or accelerated phase CML, PFS data were immature with less than 50% of subjects having progressed or died. In Cohorts E and F, median PFS was 169 days (5.6 months) and 98 days (3.2 months) respectively.

Overall survival (OS)

For patients with chronic or accelerated phase CML, OS data were immature (<50% of subjects had died). In Cohorts E and F, median OS was 6.9 months and 6.6 months, respectively.

Delegate comment: The lack of randomisation and the immaturity of the data limit the conclusions that can be drawn about PFS and OS. The Phase III trial designed to address this was discontinued due to the adverse event rate[58] (see below).

Subgroup analyses

Delegate comment: Due to being performed on subgroups, the following findings are exploratory only.

- Response rates tended to decline with increasing number of prior TKIs, longer time since diagnosis and in CP-CML, response rates tended to decline with increasing age
- Response rates were similar in patients who were either resistant to or intolerant of prior dasatinib/nilotinib

[58] Due to the adverse event rate in the ponatinib clinical program.

- In CP-CML, cytogenetic response rates were significantly higher among subjects who had the T315I mutation (with no other mutation) compared with other mutation subgroups.

  Delegate comment: Those with the T315I mutation may be less heavily pretreated as having this particular mutation was a separate entry criterion.

Other analyses

A post hoc multivariate logistic regression analysis (report no ARP307) explored the effect of dose intensity and several baseline prognostic factors (age, time since diagnosis, number of prior TKIs, T315I mutation status, baseline neutrophil and platelet counts and weight) on efficacy outcomes. The main efficacy findings of this analysis were:

- The clinical evaluator noted that for patients with CP-CML, the probability of achieving a MCyR after 12 months significantly increased with increasing dose intensity (as measured by average daily dose) ($p < 0.0001$) and with decreasing age ($p=0.0458$). This was deemed contrary to the original subgroup analysis (see above) as T315I mutation status was not a significant predictor of efficacy, after adjustment for dose intensity and other factors.

  Delegate comment: After 12 months the effect of T315I as a predictor of response could be diluted by an earlier MCyR response rate in this group, confounded by the number of lines of prior treatment as well as this being an analysis with relatively small numbers. Randomised controlled data would be required to clarify this issue further.

- For patients with advanced/blast phase CML or Ph+ALL, the probability of achieving a MaHR at 6 months increased significantly with increasing dose intensity ($p < 0.0001$) and baseline disease severity ($p= 0.0046$).

  Delegate comment: This indicates the need to maintain higher starting and maintenance doses in these groups, despite the risk of adverse events (See Starting dose and Dose Reduction in Safety section).

Supportive efficacy study - Study 101

This was a Phase I, open, dose-escalation trial with a conventional '3+3' design, conducted in subjects with advanced haematological malignancies, including subjects with CML and Ph+ ALL.

Primary objective: to determine the maximum tolerated dose (MTD) or a recommended dose of oral ponatinib.

Key secondary objectives were to examine the safety, the anti-leukemic activity, and the PK/PD of ponatinib.

The inclusion criteria were any haematological malignancy except lymphoma for further details of both inclusion and exclusion criteria.

Sixty patients with CML and 5 with Ph+ ALL (out of a total of 81 patients) received ponatinib as a once daily dose, with a 28-day 'cycle' with no breaks between cycles. Some 93.8% had already been treated with at least 2 TKIs and 63.1% had received at least 3 TKIs. Most subjects discontinued these drugs due to disease progression or lack of response, and approximately 20% due to intolerance. Some 29.2% had the T315I mutation.

The main efficacy variables, measured only in the CML, AML or Ph+ ALL patients, were:

- Cell counts in peripheral blood and bone marrow, and the presence or absence of extramedullary disease (for example, splenomegaly and hepatomegaly)
- The presence or absence of cytogenetically abnormal cells (for example, Ph+ve cells) in metaphase in bone marrow.

For CML and Ph+ ALL, the levels of BCR-ABL ribonucleic acid (RNA) transcripts relative to ABL RNA transcripts, in buffy-coat blood cells, as measured by quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR).

Only those in CML or Ph+ ALL are discussed here. At the time of analysis, the median duration of follow-up was 19.4 months (range 2.1 to 164.4 weeks).

Chronic phase CML (CP-CML)

Some 97.7% of these subjects either maintained or achieved a complete haematological response (CHR), 65.1% achieved or maintained a complete cytogenetic response (CCyR) and 44.2 % achieved a major molecular response (MMR).

Response to therapy improved with longer duration of treatment (for example, MCyR was 45.2% after 3 months of treatment and 66.7% after 12 months). All response rates were higher in patients with recently diagnosed disease (<5 years duration) compared with those with longer time periods since initial diagnosis. Response rates were higher in subjects with the T315I mutation compared with subjects with different or no mutations. The median time to MCyR was 12.3 weeks (range: 3.1 to 156 weeks) and the median duration of MCyR had not been reached. Median time to MMR was 113 days (range: 54 to 682), and the duration of MMR ranged from 16 to >129 weeks (median not yet reached).

Advanced phase Ph+ leukaemias

The numbers of patients were small: AP-CML, 9; BP-CML, 8; and Ph+ALL, 5. The median duration of MaHR was 15.7 weeks (range 3.6 to 64.0). The median time to MCyR was 72 weeks (range: 2 to 112 weeks) and the median duration of MCyR had not been reached. Only 2 of the 22 subjects achieved a MMR which was transient for both: 8 weeks (AP-CML), and 4 weeks (Ph+ALL).

Efficacy was improved with increasing AUC.

An updated efficacy summary for Studies 101 and 201 with a cut-off of 6 January 2014 was provided. This included 5 non-cohort assigned patients in the CP-CML and AP-CML arms and show the results now with a median survival of 28 months (0.1 to 40) compared with the best response with the prior therapy.

Efficacy summary

The Delegate is in agreement with the clinical evaluator that the data are considered adequate to establish the efficacy of ponatinib. In two open-label, non-comparative studies, efficacy has been established in patients who were heavily pre-treated with imatinib, dasatinib and/or nilotinib; all currently registered TKIs (although nilotinib is not currently registered for Ph+ ALL or BP-CML; see Table 1). As only a limited number in Study 201 had received prior bosutinib and there has been no head to head comparison (registered in Australia in April 2014 for CML but not Ph+ ALL), it is not possible to comment upon the relative efficacies of these 2 agents.

These findings support the demonstration of efficacy of ponatinib in those:

- in whom dasatinib or nilotinib have failed, after prior imatinib therapy.
- who harbour the T315I mutation in BCR-ABL, which is associated with resistance to currently available TKIs.

This was endorsed by the Haematologist from whom the Delegate sought advice.

Safety

No studies assessed safety as a primary outcome. Safety data were evaluated from Studies 101 and 201, and the Phase III study (ponatinib versus imatinib in newly diagnosed CP-

CML) terminated on safety grounds. The clinical pharmacology studies only consisted of a single dose administered to healthy volunteers so were very limited.

Four reports were presented for the pooled safety database during the course of the submission:

First round clinical evaluation

1. The Summary of Clinical Safety (SCS) which included safety data collected up to the data cut-off dates for the two studies (23 March 2012 for Study 101 and 27 April 2012 for Study 201)
2. A '120-day update' which included safety data collected up to 23 July 2012
3. An addendum to the clinical overview provided in response to the FDA safety concerns (cut-off 3 September 2013). This mostly provided updated data on vascular adverse events from Study 201 but also included some data on cardiac failure, ocular toxicities and neuropathy.

Second round clinical evaluation

4. A further update of safety data (cut-off of 6 January 2014), predominantly focused on vascular AEs, and which included:
   - 3 new clinical trial populations in addition to 101, 201
   - response to the questions raised by the EMA following the temporary suspension of marketing
   - safety data from 101, 102, a study in Japanese subjects, in GIST and the discontinued Phase III EPIC study
   - responses to clinical questions from the first round clinical evaluation

   Delegate comment: The serial presentation of safety data with updates restricted to specific adverse events, as well as variously reporting on a specific trial or introducing new populations with less exposure, presents some challenges in understanding the rates of all AEs, and in particular for determining the risk over time with longer duration of exposure to ponatinib.

The 120 day update included updates of pooled safety data, common adverse events (that is, not necessarily treatment related) but no breakdown of common treatment-related adverse events, that is, those attributable to ponatinib. The fourth update with a cut-off of 6 January 2014, included pooled data from the more mature Phase I and II studies combined with the discontinued Phase III EPIC study (imatinib versus ponatinib), as well as a pooled analysis of all studies including the immature studies in GIST and a Japanese study. Inclusion of these studies with shorter duration has lowered the adverse event rates. These last data were assessed for any new signals but the pooled data are not able to be compared with previous data sets.

In the five submitted clinical studies in the SCS, a total of 530 patients and 53 healthy volunteers received at least one dose of ponatinib. Of the 530 patients, 514 had CML or Ph+ALL (the proposed indication) and 16 subjects (all in Study 101) had other haematological malignancies. The pooled safety database included all 530 patients.

Randomised data providing safety information – Study 301, Phase III EPIC trial.

This open-label trial with two parallel groups randomised *newly diagnosed* CP-CML (1:1) to receive either ponatinib 45 mg or imatinib 400 mg once daily (the approved dose for initial treatment of chronic phase CML). This was terminated after 15 months due to the rates of vascular AEs with ponatinib. At the time of study discontinuation, 153 subjects had received ponatinib and 150 had received imatinib for a median of 114 days and 140

days, respectively; only 23.6% of ponatinib subjects and 31.4% of imatinib subjects had received at least 6 months of treatment.

The safety data from this study, submitted at the request of the TGA, are useful only for defining the short-term toxicity of ponatinib compared with imatinib, a marketed agent from the same class with a well-defined safety profile. The data indicate that overall, ponatinib is a more toxic agent than imatinib with a notably higher incidence of Grade ≥ 3 AEs (59% versus 27%), serious AEs (30% versus 9%), treatment-related AEs (22% versus 3%) and withdrawals due to AEs (10% versus 2%). It is associated with a higher risk of hypertension (17.0% versus 1.3%), pancreatic toxicity (5.2% versus 0), hepatic toxicity (17% versus 8%), and skin (all grades 61% versus 37%; Grade 3/4 10% versus 2%) and eye toxicity (38% versus 18%, though most were Grade 1 or 2).

The data also suggest ponatinib is associated with more serious vascular events, Grade 3 or 4 thrombocytopenia and an increased incidence of heart failure, although the duration of treatment was probably too short to expose this last risk.

Adverse events

Ponatinib was associated with a higher incidence of:

- Dermatological toxicity: rash (36.6% versus 16.7%), dry skin (17.0% versus 3.3%), alopecia (11.1% versus 5.3%), pruritus (11.1% versus 7.3%)
- Hypertension (17.0% versus 3.3%)
- Headache (32.0% versus 12.7%)
- Thrombocytopenia (22.9% versus 12.0%)
- Pancreatic toxicity: elevated lipase (26.8% versus 7.3%); elevated amylase (9.8% versus 0.7%)
- Abnormal LFTs: elevated ALT (11.8% versus 1.3%); elevated AST (10.5% versus 4.0%)
- Some gastrointestinal tract (GIT) toxicities: abdominal pain (34.6% versus 10.0%); constipation (26.1% versus 2.0%).

Imatinib was associated with a higher incidence of periorbital oedema, nausea, vomiting, diarrhoea and muscle spasms. Analysis of treatment related common AEs gave a similar pattern.

Serious AEs

A summary table of SAEs that occurred in at least 2 subjects was presented. Notably, there were 5 cases of pancreatitis in the ponatinib arm and none in the imatinib arm. Serious events of decreased platelet count, atrial fibrillation, acute myocardial infarction and cardiac failure were also increased in the ponatinib arm.

Delegate comment: There are significant sources of bias, potentially in favour of the more toxic treatment, in presenting the data in this way, as follows:

a. The apparent number of SAEs has been lowered in this table as MedDRA terms for clinically related or indistinguishable events have not been collated; for example it lists one case of 'peripheral artery thrombosis' separately from one of 'peripheral arterial occlusive disease'; thus, these are considered separate clinical events and do not appear in the summary SAE table.

b. With such brief data collection period, particularly in a trial terminated because of toxicity, limiting the summary to events occurring in ≥2 patients has led to an underrepresentation of the spectrum of SAEs, such as single additional clinically

important events only occurring in the ponatinib arm included one case of retinal vein thrombosis and one of angina pectoris.

Treatment-related adverse events (adverse drug reactions) from pooled safety data (Studies 101, 201)

The treatment related AEs were 90.9% (120 day update) in this heavily pretreated population with advanced disease. There was no updated table of common treatment-related adverse events (>5%) provided in the 120-day safety update, thus the figures in the CER are from an earlier cut-off. Subsequent safety data submitted examined specific adverse events, predominantly vascular.

The incidence of total SAEs (at the July 2012 cut-off) was 56.2%, of which 22.6% were considered treatment-related. These were more common with advanced disease and while many were consistent with disease progression (for example, disease progression, blast crisis), others could be either related to the disease or the treatment, for example myelosuppression, infections.

Delegate comment: In the absence of randomised, controlled data, it is not possible to determine the background rate of adverse events and make attributions about causality. These figures require updating as several safety updates have been provided since these data were submitted (see Questions for sponsor).

Withdrawals due to AEs

In the Phase III trial, treatment-related discontinuations were higher with ponatinib (15) compared to imatinib (3). Most of these were decreased platelet count (4), abdominal pain (3), abnormal LFTs (2) and rash (2). All other AEs leading to discontinuation occurred in a single patient each. The sponsor is requested to clarify how many patients experiencing an SAE in this trial were able to recommence ponatinib and whether these were included in the treatment discontinuations (see *Questions for sponsor*).

The sponsor's reported incidence of AEs leading to treatment discontinuation at the time of the 120-day safety update for Studies 101 and 201 was 17.9%, with treatment-related discontinuations reported as 8.3%.

Delegate comment: The figures for Studies 101 and 201 need to be updated as treatment-related discontinuations are a highly significant clinical event in the context of an incurable disease with few remaining treatment options (see Questions for sponsor). The sponsor has stated in the PI that Study 201 had 50/449 (11%) discontinued due to AEs, with 37/449 treatment-related (8.2%). The sponsor is requested to explain whether these figures are from the 120 day cut-off, and if so, to update these and include in the PI in the adverse events section.

Dose reductions with adverse events

At the 120 day update, the median duration of treatment was 323 days (10.6 months). 349 subjects had been treated for at least 6 months and 185 subjects for 12 months. 51.5% of subjects had required dose reduction, with the median daily dose being 36.5 mg as opposed to the starting daily dose of 45 mg. Although potentially skewed by the low starting doses in the Phase I study, the absolute and relative dose intensities indicate that the more advanced phases were treated with higher doses for longer and the median dose in the CP-CML was lower than for either of the more advanced phases. The latest updated safety analysis from 6 January 2014 cut-off (including Phase I, II and III ponatinib trial exposure) indicates the dose reduction rate to have increased to 76.6% (even with the newer shorter duration trial data) in the CP-CML population. Dose interruptions and reductions were similar for the AP-CML (68.1% and 64.8%, respectively) while interruptions (39.3%) were more common than reductions (21.5%) in the BP-CML/Ph+ ALL consistent with the need to maintain the higher dose for efficacy.

Delegate comment: These findings reflect that higher doses were required for initiation and maintenance of a response, particularly in advanced disease. The number requiring dose reductions indicates a very narrow therapeutic range but also suggests that the MTD was not adequately established, particularly for the CP-CML population. The sponsor has indicated that a Phase II study is planned to investigate the effect of differing doses in CP-CML who have had two prior TKIs. A different capsule sizing might have provided greater dosing flexibility.

Starting dose

The sponsor proposes to retain the starting dose because the data indicate that the efficacy of ponatinib increases with increasing dose. The use of the 45 mg dose (the MTD) as the starting dose maximises the chance of achieving a response. The sponsor has indicated that it will be conducting a new Phase II study examining starting doses of 15, 30 and 45 mg/day in subjects with refractory CP-CML (company study report (CSR) expected June 2019).

Dose reductions

The PI contains advice regarding lowering doses in adverse events. Updated data in the 59 CP-CML subjects who achieved a MCyR on 45 mg but required a dose reduction after an AE, indicates all maintained their response on 30 mg daily and 97% of the 29 subjects with a MCyR on 30mg maintained that at the lower dose level. Duration of dose reduction did not affect the maintenance of response. The Delegate supports consideration of a dose reduction in CP-CML subjects who achieve a MCyR, especially where there are risk factors for adverse vascular events. However, dose reductions in those with more advanced disease were commonly associated with a loss of response and the Delegate is in agreement that the risk-benefit equation for these patients justifies maintaining the starting dose where possible.

Delegate comment: Currently the US PI contains advice regarding dose reductions for those with CP-CML *and* AP-CML who achieve a MCyR. Expert clinical advice from a haematologist was for a dose reduction to be considered after a period of 3 months but only for the CP-CML patients who achieve a MCyR. The sponsor is requested to make specific recommendations about the dose levels to be considered and include these in the PI.

Laboratory abnormalities as AEs

Myelosuppression occurred in 28% of subjects on ponatinib and 22% of subjects on imatinib. Thrombocytopenia was more frequent with ponatinib while other cytopenias were more common with imatinib. Elevations of lipase and amylase were more common with ponatinib, consistent with the increased incidence of pancreatitis. Elevations of transaminases were also more common with ponatinib. Decreased phosphate was notably more common in the imatinib arm.

AEs of special interest

For the early trials, these were identified on the basis of their association with BCR-ABL TKIs or with CML-Ph+ and included: myelosuppression, infections, bleeding events, pancreatic events, hepatic events, cardiac events, ischaemic vascular events, oedema and fluid retention events, skin and subcutaneous tissue disorders. In subsequent safety updates following submission, the focus became the vascular occlusive events.

Vascular AEs

The Phase III (301) trial was discontinued due concerns over the rate of vascular AEs

Study 301

While the total incidence of vascular events was only slightly increased in the ponatinib arm (8.5% versus 6.0%), the rate of serious vascular AEs was much higher with ponatinib (4.6% versus 0.7%). Both the short duration of treatment in this trial and the earlier stage of disease in this trial population (with lower background risk) is likely to explain the much lower incidence of 8.5% compared with Studies 101 and 102 (35% and 22.5% respectively - see below).

Study 201

Those with a recent myocardial infarction or unstable angina were excluded from Study 201.

At the updated 6 January 2014 cut-off, 38% of subjects remained in the study, and 22.5% had experienced at least one vascular occlusive adverse event, and in 16.0%, at least one of these events had been considered serious.

> **Delegate comment**: The total rate of 22.5% is not mentioned in the PI and the 16% SAEs are divided across several different events. These numbers need to be presented clearly in the Precautions section of the PI and also in a boxed warning.

In the earlier analyses (cut-off September 2013), the sponsor identified that arterial AEs were strongly associated with higher dose intensity (as measured by the average dose up to the date of the event), increasing age, a medical history of diabetes and a medical history of ischaemia. Vascular events, particularly thromboembolic events occurred more frequently in subjects with advanced stage disease.

> **Delegate comment**: The risk appears to be related to dose-related should be included in the PI under the Vascular Occlusion, Precautions.

Updated data were also presented demonstrating that subjects who experienced an arterial AE had comparable survival and Progression free survival (PFS) with those subjects who did not experience such an event, but this assessment did not incorporate a quality of life assessment or comment on any sequelae, particularly from SAEs.

Study 101

At the updated 6 January 2014 cut-off, 30% remained in the study. The sponsor reported the overall incidence of vascular AEs was 35%, which is notably higher than that in the pivotal study above (22.5%). The difference was due to a higher incidence of cardiovascular events (21% versus 10%). The incidence of cerebrovascular, peripheral vascular and venous events was comparable in the two studies. The incidence of vascular serious AEs was 23%.

> **Delegate comments**: These Phase I figures are not included in the PI; the lower rates have been included from the Phase II study. Both the total (35%) and the SAE (23%) should be included. They may be higher due to the longer duration of treatment.
>
> a. The rate of vascular adverse events is very high and in the majority, they were severe. Therefore, the Delegate is in agreement with the clinical evaluator that this warrants inclusion in the PI as a boxed warning.

Important discrepancies in reporting of adverse vascular event rates

The clinical evaluator noted discrepancies between incidence figures quoted in the updated safety report (September 2013 cut-off) and those in the US prescribing information approved on 20 December 2013:

- All arterial AEs: 77/449 (17.1%) versus 91/449 (20%) in the US PI
- Cardiac arterial AEs: 41/449 (9.1%) versus 55/449 (12%) in the US PI

- Cerebrovascular arterial AEs: 26/449 (5.8%) versus 27/449 (6%) in the US PI
- Peripheral arterial AEs: 28/449 (6.2%) versus 36/449 (8%) in the US PI.

The sponsor provided a copy of a communication with the EMA (dated 31 October 2013) addressing differences between the FDA and sponsor analyses. It stated that the FDA had not provided the sponsor with details of their incidence calculations. However, the FDA had appeared to use a broader set of AE terms than the sponsor for inclusion in their analysis (for example, Cardiac arrest, Cardio-respiratory arrest, Chest discomfort, Clumsiness, Electrocardiogram T Wave Abnormal and Encephalopathy).

The clinical evaluator noted that the FDA had determined that the incidence of vascular AEs in Study 101 was 48%. In response to the clinical evaluator's question, the sponsor has indicated that the FDA had not explained to the sponsor how this figure was derived. However, the sponsor believes that the figure was based on the subpopulation of patients with CML/Ph+ ALL (n=65) (who are relevant to the proposed indication) rather than the entire population (n=81), and that the following AE terms were included in the FDA analysis (but not in the sponsor analysis); Arteritis, Cardiac arrest, Cardio-respiratory arrest, Chest discomfort, Clumsiness, Electrocardiogram T Wave Abnormal, Encephalopathy, Haemorrhagic Vasculitis, Non-cardiac chest pain, Peripheral Coldness, Phlebitis, Raynaud's Phenomenon, Renal Artery Stenosis, Vasculitis and Visceral Arterial Ischaemia.

Delegate comment 1:The EMA requested broader MedDRA terms be used to capture vascular AEs but the Delegate notes that these vascular occlusive terms still excluded relevant events such as renal artery stenosis, visceral arterial ischaemia and cardiac arrest (the sponsor has postulated that these terms were among a range included in the FDA analysis). Thus it is still unlikely the sponsor has captured all the relevant vascular or cardiac events, and by excluding terms such as 'cardiac arrest', the sponsor's figures may underestimate their severity. This may account for the ongoing difference between the sponsor's figures and those from the FDA. The mechanism of the cardiac/vascular damage is not yet understood, but the nonclinical studies indicated direct damage, for example myocardial fibrosis/necrosis and there is also a significant elevation in blood pressure. Inflammatory changes have not been ruled out. Ponatinib has effects that include targeting members of the VEGFR family and the sponsor postulates that there may be endothelial damage. The Delegate considers it important to include all the terms thought to be used by the FDA to reconcile potential differences and clarify the adverse event rates. Therefore, the sponsor is requested to do this for the pre-ACPM response and to provide a justification for not including any such terms and for any differences in the rates they propose to include in the Australian PI compared with the US PI. The Australian PI will also need to include a statement as to there being differences between rates reported in the PIs; the sponsor is requested to provide wording for this and the ACPM is requested to provide advice on this matter, taking into account the sponsor's pre-ACPM response. The ACSOM identified consistency in the information presented between the PIs about the risks as very important, particularly with the availability of information from a range of sources including the sponsor's website which links to the US PI.

Delegate comment 2: The US PI presents a very clear section under 'Vascular Occlusion' that advises the prescriber about the rates and risks of vascular occlusive events, broken down into arterial occlusion and thrombosis and venous thrombosis. It lists total rates, time to onset and so on and a table that breaks down the rates of such AEs by age and risk factors. The sponsor is requested to present the information for the Australian PI in this informative way, using the same format.

Heart failure

Study 301

Four (2.6%) patients developed cardiac failure in the ponatinib arm and 1 (0.7%) in the imatinib arm. LVEF was monitored using echocardiography, although the short duration of time of this trial is likely to underestimate the risk of cardiac failure over time, particularly where linked to vascular occlusion and ischaemia. Within the short duration of the trial, the rates of heart failure with ponatinib were higher than imatinib, which is known to be associated with heart failure. Of note: the decline in LVEF (noted in Integrated safety summary, cut-off January 6, 2014), tended to occur early in treatment (1 to 3 months), while cardiac failure rates increased over a longer time.

Study 201

The overall incidence of heart failure AEs in the pivotal study was 8.0%, and 5.1% were an SAE. There were 4 deaths from heart failure (10.8% of those with heart failure) but this was not attributed by investigators to ponatinib. 23 subjects (62% of those developing cardiac failure) also had a vascular occlusive event (all were coronary events), with 16 events (43%) occurring immediately prior to or concurrent with the cardiac failure events; these were coronary events with 10/16 being myocardial infarctions. Some 5.1% experienced a decrease in LVEF ≥20%.

> **Delegate comment**: Cardiac failure followed ischaemic events in a number of subjects. It is unclear whether the ischaemic events were attributed to ponatinib, as the subsequent cardiac failure events should also have been deemed treatment-related.

Study 101

Seven (8.6%) subjects developed heart failure, with 3 (3.7%) rated as serious. Two out of seven subjects also had a vascular occlusive event.

Other studies (GIST, Japanese Phase I/II) and postmarketing

In the two other studies presented at the second round evaluation, both of which had relatively short follow-up, the rates of heart failure were both 2.9%. In the postmarketing setting, there were 33 events of heart failure reported in 28 subjects, all considered serious.

> **Delegate comment 1**: The Delegate notes that the sponsor plans to include a warning about cardiac failure in the PI but considers that the apparent risk is so significant that this should form part of the black box warning along with vascular occlusion.

> **Delegate comment 2**: While many patients had background risk factors, it is not possible to determine that ponatinib did not contribute to the heart failure, especially when other evidence points to a causative role in vascular occlusive and cardiovascular adverse events. A number had ischaemic events preceding and likely precipitating the cardiac failure.

QT prolongation

Attention has been drawn recently to the potential risk of QT prolongation with TKIs. Subjects considered at-risk were excluded from all the clinical trials, that is, those with a prolonged QT at baseline, taking other drugs known to have an effect on QT interval and those in cardiac failure. The Phase I study did not identify an effect of ponatinib dose on the QT interval but 13 subjects (2.5%) in the pooled safety database experienced an AE of QT prolongation, 1 of which was considered serious (July 2012 cut-off). No QT prolongation >500msec was reported in the Phase III study but there were some cases of mild prolongation (>30msec, >60 msec). No Thorough QT study that meets the EU Guidelines adopted by the TGA was presented and therefore an effect on the QT interval has not been excluded by the studies to date.

Delegate comment: Given the high risk of cardiac ischaemia and failure which may also prolong the QT interval, the advice of the ACPM is sought as to whether a formal Thorough QT study should be undertaken, and whether this should be a condition of registration.

Hypertension

Study 301

Significant hypertension was more common with ponatinib than imatinib: 15.7% versus 4.0% had a systolic blood pressure (BP) ≥ 160 mmHg while 7.2% versus 2.0% had a diastolic BP ≥ 100 mmHg.

Study 201

The US PI reports 67% subjects experienced treatment-emergent hypertension, with 39% experiencing Grade 3/4 severity and 2% as an SAE, including hypertensive crisis. The Australian PI lists the treatment-related rates as much lower e.g. 7% any grade for CP-CML compared to 68% treatment-emergent in the US PI for the same cohort. The sponsor is requested to explain why so few cases of the total were attributed to ponatinib.

Delegate comment: Hypertension was very common with ponatinib and in some cases severe, requires regular monitoring and management. This requires communication via a heading under the Precautions section (following the vascular occlusion and cardiac failure headings) especially given its potential contribution to those other events.

Delegate comment: The following support a causative role for ponatinib in causing vascular occlusive events:

a. The nonclinical data, where myocardial fibrosis and necrosis were observed.
b. The risk of an adverse vascular event appears proportional to dose.
c. Those with pre-existing risk factors (for example ischaemic heart disease, diabetes) were identified as having a much higher risk.
d. Significant rises in systolic and diastolic BP occurred with ponatinib.
e. There was an increasing rate of various vascular occlusive or cardiac adverse event with duration of exposure (Integrated safety summary, cut-off January 6, 2014), presented using the broad range of MedDRA terms. This examined the rate of initial adverse events in cohorts by duration of treatment. For those terms indicating a vascular occlusive process, there is a gradual increase in incidence over time, generally peaking in the 6 to 12 or12-<24 month window. This is clear for myocardial infarctions, cerebrovascular events and becomes more evident when MedDRA terms that indicate similar events are collated for example peripheral ischaemia, peripheral artery stenosis, peripheral artery occlusive disease, intermittent claudication; cardiac failure and cardiac failure congestive.

In order to capture this risk over time, the sponsor is requested to present data from the table *Incidence rate of AEs by time of initial onset for all patients treated with ponatinib* (Integrated safety summary, cut-off January 6 2014) using the collated MedDRA terms for vascular events as requested by the EMA plus those terms the sponsor indicates may have been used by the FDA, in the pre-ACPM response and incorporate these into the PI. It is noted that this table only addresses first events. The sponsor has also been requested to present data using the same collapsed MedDRA terms to identify those individuals experiencing more than one event.

Pancreatic events

Studies 101, 201 and 301

Pancreatic acinar damage was noted in the nonclinical studies, and pancreatitis was a dose-limiting toxicity in the Phase I study. Prior to termination in the randomized trial there were 5 cases in the ponatinib arm and none in the imatinib arm and 25.3% of subjects in the pooled safety database (Studies 101 and 201) experienced a pancreatic AE, most commonly, an elevation of lipase (17.9%). In Study 201, pancreatitis occurred in 7.4% of subjects and was considered an SAE in 5.8%. Most cases were manageable with a dose interruption or reduction, with only 5 subjects (0.9%) discontinuing. While the sponsor indicated that pancreatitis tended to occur early on with treatment (72% within the first 30 days in Study 201), new cases continued to be reported throughout the treatment periods in Study 301 while elevations of serum lipase were seen throughout the treatment duration period without an apparent pattern. The Delegate suggests regular monitoring, not 'periodically' as stated in the PI.

> **Delegate comment**: Pancreatitis is known to occur with other BCR-TKIs but the rate appears much higher with ponatinib. Long term effects on the pancreas are not known.

Infections

Study 301

While infection rates were comparable between the two arms (28% with ponatinib and 29% with imatinib), Grade 3/4 infections were more common with ponatinib (5% versus 2%).

Bleeding events

Study 301

There were fewer bleeding events in the ponatinib arm (7.2% versus 12.0%) than the imatinib arm in the Phase III trial. Some 25.8% experienced a bleeding event in Study 201; 1of the 7 deaths due to bleeding events was considered treatment related. Thrombocytopenia was a common AE with ponatinib.

Hepatic events

Study 301

Hepatic adverse events were more common with ponatinib (17% versus 8%). As described above, elevations of transaminases on laboratory testing were also notably more frequent with ponatinib. No cases of hepatotoxicity meeting Hy's Law criteria were reported.

Pooled safety database (Study 101 and 201, July 2012)

The incidences for hepatic AEs were: 27.2% all hepatic AEs, 10.2% Grade 3 or 4, 1.1% SAEs.

Two cases met Hy's Law criteria for drug-induced liver injury (DILI).

The clinical evaluator regarded as suspicious of severe DILI, a case from the Japanese Phase I/II studies in Ph+ ALL discussed in the second round clinical evaluation. It is stated in the 120 day update that a liver necropsy was pending and the sponsor is requested to provide the result of this in the pre-ACPM response. The potential for severe liver injury with ponatinib requires a clear warning in the PI.

An additional case report for one patient who died from acute liver failure contained insufficient information for the clinical evaluator to assess causality.

> **Delegate comment**: These are 2 of the 3 cases of death due to liver failure that are listed in the US PI. The third was not considered by the clinical evaluator to be

attributable to the study drug. Liver function needs to be monitored regularly, not 'periodically' as stated in the PI.

Dermatological toxicity

Study 301

Skin events occurred in 61% of ponatinib subjects compared to 37% of imatinib subjects. Grade 3 or 4 events occurred in 10% versus 2% respectively and were a cause of discontinuation for 2 patients in the ponatinib arm.

Study 201

Updated safety data have not been provided but the rate in the initial Summary of Clinical Safety (SCS) indicated incidences of 75.1% all grades, 9.6% Grade 3/4, SAEs 2.8% and discontinuations 0.9%.

Ocular toxicity

Study 301

Eye disorders occurred in 38% of ponatinib subjects compared with 18% of imatinib subjects, mostly Grade 1 or 2. Grade 3 or 4 events occurred in 1 ponatinib subject (eye pain) and 2 imatinib subjects (vitreous haemorrhage for both).

Study 201

Serious vision threatening ocular toxicities were reported in in **3%** of patients in the 3 September 2013 update including macular oedema, retinal vein occlusion and retinal haemorrhage have occurred. Serious ocular AEs that were considered related to ponatinib were cystoid macula oedema (1 case) and retinal vein thrombosis (1 case). This needs to be included in the PI under Precautions.

Neuropathy

The safety update up to 3 September 2013 (Study 201 only) reported neuropathy (peripheral or cranial) for 14.5% subjects; the incidence of treatment-related neuropathy was 6%. 5.6% were Grades 2 or 3. This needs to be included in the PI under Precautions.

Other – Adverse events reported to the TGA

The TGA received adverse event reports for two subjects, both of whom experienced multiple serious AEs. A clinical trial participant experienced bilateral cystoid macular oedema, then at a later date a popliteal artery complicated by bilateral cerebral infarcts due to emboli from an ulcerated atherosclerotic plaques. The sponsor is requested to present in graph format, the proportion of patients participating in Studies 101 and 201 who experienced a single SAE, 2 SAEs or >3 SAEs.

Delegate comment: There were no quality of life data, which given the severity of these events, would be important in providing the patients' perspectives on the impact of these AEs and the significant risks associated with taking ponatinib.

Safety discussion

There is compelling evidence to point to ponatinib having a causative role in a range of adverse events; there high rates of vascular occlusive and cardiovascular adverse events, including cardiac failure, some of which were fatal. There was a predominance of arterial vascular adverse events. The risk increases with dose, dose intensity, duration and is higher than that seen with imatinib. Predisposing factors for cardiovascular disease, including increasing age, diabetes and hypertension, were identified as independent risk factors as well as dose intensity and advanced disease.

The product information documents for the other BCR-ABL TKIs registered in Australia all list vascular adverse drug reactions (that is, treatment related vascular AEs). They are described as being uncommon (incidence 0.1% to 1.0%) or rare (incidence < 0.1%). Peripheral arterial occlusive disease is an adverse effect of nilotinib, but the incidence of treatment related vascular AEs with ponatinib suggests that the frequency of such events is notably higher with this drug, and the limited randomised data confirm this compared with imatinib.

Both the incidence and the severity of the vascular/cardiovascular adverse events including cardiac failure warrant inclusion of these in a black box warning. It is noted that the ARIAD website for Iclusig cites boxed warning. The FDA boxed warning also includes hepatotoxicity and the sponsor has been requested to provide details of the case where severe DILI remains a potential cause of death. Other information provided by the sponsor regarding cases of hepatotoxicity did not have sufficient detail to permit evaluation. The advice of ACPM is sought on whether this should also be included in the boxed warning, given the relatively small number of subjects treated with ponatinib in the clinical trial setting.

Additional adverse events seen at a much higher rate with ponatinib than other BCR-ABL TKIs include pancreatitis.

As evidenced by the orphan designation, CML and ALL are rare diseases, and ponatinib and its side effects will not be known outside this highly specialised area. With vascular occlusive events estimated at 48% by the FDA and given the high likelihood of an emergency/out of hours presentation with such events, it is essential that these risks be conveyed to health care professionals most likely to be assessing these patients such as Accident and Emergency. In order to facilitate a more rapid diagnosis and management, it is imperative that health care professionals are promptly made aware of the potential side effects of ponatinib. The most effective way for this is for the patients to carry an information card and the Delegate is in agreement with the RMP evaluator that the sponsor should provide this and considers this should be a condition of registration. Many institutions provide such a card for neutropenia, a well-recognised side effect of chemotherapy, but both the rarity of ponatinib usage and the frequency and severity of vascular occlusive events justify this measure.

The mechanism underlying these adverse events remains unclear but may include the broader range of action beyond BCR-ABL and the sponsor is planning to conduct a study looking at 3 dose ranges to determine the safety and efficacy in refractory CP-CML.

Efficacy and safety summary conclusions

There are no randomised clinical trials to establish the efficacy of ponatinib improvement for the sponsor's proposed indication and thus no demonstration of improved survival. The only Phase III trial that would have provided this information was terminated early due to the increased adverse events. Durable responses have been demonstrated with ponatinib use in heavily pre-treated patients with CP-CML and to a lesser extent those with accelerated or blast phase CML and Ph+ ALL. It is effective against the treatment emergent T315I mutation which confers resistance to other TKIs. There have been significant treatment-related adverse events and there are no quality of life data.

Ponatinib has significant toxicities, which are not fully characterised due to the lack of evidence from randomised controlled trials following the termination of the Phase III EPIC trial of ponatinib versus imatinib due to adverse events. Thus most of what is known about the safety, including all the longer term usage data, come from the open label, single arm Phase II study and the Phase I dose-finding study. This makes attribution of causality difficult especially in those with advanced disease in whom the background rate of events would also be significant.

Therefore, it is not possible to establish the incidence of treatment-related events with any certainty. There remains a discrepancy between the FDA's and the sponsor's figures regarding the incidence of treatment-emergent vascular occlusive and cardiac adverse events, and the proportion attributable to ponatinib. Ponatinib is clearly associated with a markedly increased risk but understanding the magnitude of that risk is critical to ensure prescribers are able to convey this information so that patients make a fully informed decision as to whether the benefits outweigh the risks for them as individuals. This issue appears to have arisen largely through both the use of different MedDRA terms and attribution of causality, the sponsor has been asked to address this in the pre-ACPM response, so that the PI and CMI can accurately reflect the risks. The ASCOM considered it important that this discordance between the US and Australian PI be addressed.

Safety measures

Boxed warning

An integral part of conveying this information clearly to prescribers and patients is the use of a boxed warning for both the vascular occlusive and cardiac failure risks. The wording of this could be taken from the US boxed warning, with an incidence for the adverse event rates to be presented and justified by the sponsor. Both the Delegate and the clinical evaluator consider this essential and thus it is a condition of registration. The advice of the ACPM is sought regarding whether hepatotoxicity should also be included.

Patient/doctor information card

An additional important safety measure is a patient information card to alert treating health care professionals of the potential risks of ponatinib to ensure rapid triage, appropriate investigation and management of those taking ponatinib who present acutely unwell. This was endorsed by the haematologist from whom the Delegate sought expert advice, as many patients will present with acute chest pain or acute abdominal pain and are most likely to be assessed by an emergency doctor, and provision of this information may be life-saving. This is a condition of registration.

Use of ponatinib to be for those under the care of a Haematologist

Subjects should only be commenced on ponatinib after a careful risk-benefit assessment which has included consideration of transplantation or other TKIs and expert opinion has confirmed the Delegate's view that this requires care under a haematologist. Similarly, ongoing monitoring should be by a haematologist as consideration of dose reduction in the chronic phase CML following a response or discontinuation if no response is recommended and requires expertise to make these assessments. It was considered that by the time patients are at this point of needing ponatinib, that is, have resistant/progressive disease or documented T315I mutation or severe complications of previous TKI therapy, they would be under the care of a haematologist, who has the requisite expertise in managing these rare adult leukaemias.

Risk management plan

RMP evaluation

The Office of Product Review has accepted the EU-RMP, version 9.0, dated 4 June-2014, data lock point 6 January 2014, and is awaiting the Australian Specific Annex (subsequent to version 2.0), to be submitted with the pre-ACPM response.

The opinion of the ASCOM was sought on 7 March 2014.

A number of recommendations for the RMP have been provided by the RMP evaluator and the sponsor should address these matters in the Pre-ACPM Response and follow up where appropriate with the TGA's Office of Product Review.

Risk-benefit analysis

Delegate's considerations and proposed action

The Delegate believes that given both the seriousness of the diseases being treated and the inevitable progression without treatment, that registration is supportable for those for whom there are no other treatment alternatives. Such patients may consider the risks of treatment are acceptable given the alternative is progression of their disease unabated. However, the toxicities are significant; higher than imatinib, and within the limitations of cross-trial comparisons higher than other TKIs for vascular and cardiovascular adverse events. The risk of vascular occlusive and cardiovascular adverse effects and cardiac failure appear to be cumulative. Furthermore, there has been no proven increase in survival or improvement in quality of life. The Delegate believes it is important the TGA conveys these limitations and uncertainties in the indications by stating there is no trial evidence to indicate improved survival or quality of life data and the ACPM's advice is sought on this matter. The wording used here is taken from the US indication when granting accelerated approval, which is intended to convey the uncertainties associated with an approval in the absence of Phase III confirmatory data. These data will now not be forthcoming. Thus, the Delegate's amended indications for registration are as follows:

'*Iclusig is indicated for the treatment of adult patients with:*

- *Chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia whose disease is resistant to, or who are intolerant of at least two prior tyrosine kinase inhibitors; or where there is a T315I mutation.*
- *Philadelphia chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) whose disease is resistant to, or who are intolerant of dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or where there is a T315I mutation.*

These indications are based upon response rate. There are no trials verifying an improvement in disease-related symptoms or increased survival with Iclusig[59]*.*

Therapy with Iclusig should be initiated and monitored by a haematologist with expertise in managing adult leukaemias.'

Data deficiencies/limitations

The Product Information is currently lacking in detail, particularly total rates of events such as vascular occlusive adverse events, to inform clinicians (and thereby, prospective patients) of the risks of ponatinib for the proposed usage. Further recommendations for changes from the ACPM are sought.

The vascular adverse event data has been analysed with apparently fewer MedDRA terms which, together with differing attribution of relation to treatment, may account for the discrepancies between the sponsor's and the FDA's calculation of vascular occlusive adverse events. This needs to be reconciled using the terms the sponsor has identified as likely to have been used by the FDA and presented in the pre-ACPM summary. This was supported by the ACSOM.

[59] This sentence was subsequently removed and is not included in the approved indications (see below under *Outcome*).

No absolute bioavailability study was presented and therefore key PK data for Vd and CL are missing.

There is significant inter-patient variability in the AUC for ponatinib, which given the strategy of dose reductions to reduce the risk of side effects, suggest such variability is likely to be clinically relevant. There is not a clear explanation for this variability.

There are no evaluable data for use in subjects with hepatic or renal impairment (see *Conditions of Registration*).

There was no Thorough QTc study to assess formally the risk of QT prolongation, a known risk with a number of TKIs (for example nilotinib, a BCR-ABL TKI). Use of medications that are associated with torsades de pointes was an exclusion criterion and patients with risk factors were excluded.

There were no data on quality of life which is a significant omission given the rate of SAEs and treatment-related discontinuations (data require updating for these two outcomes).

Conditions of registration

1. Implementation of the EU-RMP, version 9.0, dated 4 June 2014, data lock point 6 January 2014, with Australian Specific Annex (subsequent to version 2.0), to be revised to the satisfaction of the TGA.
2. The development of a patient information card for patients to carry to alert health care professionals about the potential side effects of ponatinib.
3. Inclusion of a boxed warning to alert prescribers and patients of the risks of vascular occlusion and cardiac failure. The advice of the ACPM is sought regarding including hepatotoxicity, taking into account the sponsor's pre-ACPM response.
4. Submission of the following clinical trial(s) as Category 1 submissions within 6 months of completion:
    a. Study 107 examining the effect of rifampicin on PK of ponatinib
    b. Study 108 examining the effect of lansoprazole on PK of ponatinib

Summary of issues

Ponatinib is a tyrosine kinase inhibitor of BCR-ABL, VEGFR family kinases. It is the fifth in this class which includes imatinib, dasatinib, nilotinib and bosutinib but is the only one effective against the T315I mutation which emerges during treatment.

The only Phase III trial was terminated early because of adverse vascular events. As a result, there are only very limited, short term randomised data to inform about safety; these indicate that ponatinib is a more toxic TKI than imatinib and together with the safety data from non-randomised Phase I and II trials, indicate a significant risk of at least 22% serious vascular occlusive adverse events and 8% risk of cardiac failure. This vascular/cardiovascular risk appears to increase with dose level, dose intensity and duration of exposure. The FDA has independently evaluated the safety data and reported higher adverse vascular event rates than the sponsor. Thus there are lower rates of AEs proposed for the Australian PI compared with the US label.

Despite there being no randomised efficacy data to demonstrate or quantify PFS or overall survival (OS) after treatment with ponatinib, the Phase I and II data indicate that it appears efficacious after the failure of other TKIs and it remains the only TKI effective against the T315I mutation that emerges with treatment in Ph+ CML and Ph+ ALL. The recommendation below for registration is conditional upon there being a clarification of the risks in the PI as requested in the *Questions for the sponsor*. Such clarity is currently lacking to inform prescriber and patient of the risks and the sponsor has been requested

to address this in the pre-ACPM response and through post-registration commitment to undertake clinical trials.

Questions for the sponsor

1. The sponsor is requested to comment as to why there was up to 50% inter-subject variability of both C_{max} and AUC at the 45 mg/day dose.
2. What proportion of those experiencing an SAE in each of the Phase I, II and III trials resumed ponatinib treatment? Were those experiencing an SAE who were then unable to resume also included as treatment-related discontinuations?
3. The sponsor is requested to present in a graph, the percentage of patients in Studies 101 and 201 who experienced 1 SAE, 2 SAEs, >3 SAEs.
4. To clarify the discordance between the figures presented in the Australian PI and the US PI, the sponsor is requested to present the rates of vascular occlusive events (using both the EMA specified terms and those thought to be used by the FDA in reaching their figures), with a justification for any that are excluded. This information needs to be included in the PI, including any discrepancies.
5. In order to capture the cumulative risk for adverse vascular occlusive events, the sponsor is requested to present data as a graph from the table *Incidence rate of AEs by time of initial onset for all patients treated with ponatinib* in the Integrated safety summary, cut-off January 6, 2014 using the collated MedDRA terms for vascular events as requested by the EMA plus any additional terms the sponsor considers the FDA used, in the pre-ACPM response and incorporate these into the PI. It is noted that this table only addresses first events.
6. The sponsor indicated that the liver necropsy report was pending for the case of severe DILI in the Japanese Phase I/II studies in Ph+ ALL discussed in the second round clinical evaluation. The sponsor is requested to provide the result of this in the pre-ACPM summary.
7. The sponsor is requested to comment as to why so few cases of hypertension were considered treatment-related in Study 201.
8. The sponsor is requested to explain whether the figures for discontinuations due to AEs in Study 101 and 201 reported in the PI are from the 120-day cut-off, and if so, to update these and include in the PI in the adverse events section.

Request for ACPM advice

1. Whether the incidence of vascular occlusive adverse events and cardiac failure merit a boxed warning and whether hepatotoxicity should be included in the boxed warning.
2. Whether the sponsor should be required to develop a patient information card to alert health care professionals (especially in emergency setting) of the side effects of ponatinib.
3. Whether the sponsor's updated information about the vascular occlusive/cardiovascular risks in the pre-ACPM response is considered acceptable for inclusion in the Australian PI (compared to US data).
4. Whether the sponsor should be required as a condition of registration, to perform a Thorough QT study meeting the EU Guidelines.
5. The inclusion of the statement in the indication that states there is no overall survival or proven improvement in symptoms.

Pre ACPM preliminary assessment

The Delegate had no reason to say, at this time, that the application for ponatinib should be registered for the sponsor's proposed indication; however, registration is supported, for the treatment of those for whom there are no other effective treatment options either due to the presence of the T315I mutation, or due to failure or intolerance of prior BCR-ABL tyrosine kinase inhibitor therapies.

Response from sponsor

In this section the sponsor responds to the eight questions posed by the Delegate. The sponsor also notes that the Delegate is seeking advice on conditions of registration and the sponsor's position on these matters are included below.

Thorough QT (TQT) study

In response to the Delegate comments, the sponsor states that a Thorough QT study[60] for Iclusig is unwarranted based on the following data:

1. Safety pharmacology studies concluded Iclusig is not predicted to prolong the QT interval in patients
2. The QT interval was rigorously assessed (serial ECGs in triplicate, central reading, matched PK) in 39 leukemia patients in the phase 1 study who received 30 mg, 45 mg, or 60 mg Iclusig once daily. The pharmacokinetic-pharmacodynamic models show no exposure-effect relationship, and no clinically significant changes in the mean QTc interval (that is, > 20 ms) from baseline were detected in the study; and
3. In a Phase III trial comparing ponatinib to imatinib, the mean change from baseline to worst QTcF value in ponatinib was 0.1 msec (90% CI: -2.9 to 3.1); ruling out changes as large as 10 msec. On the imatinib arm (a drug not associated with QT prolongation), the mean change was 7.4 msec (90% CI: 4.0 to 10.9).

Renal impairment study

In a radiolabeled ADME study, following a single dose of 45 mg of radioactive carbon labelled [^{14}C]ponatinib, the total radioactivity recovered in faeces and urine were 86.63 ± 2.37%, and 5.38 ± 0.93% of the administered dose, respectively. Fecal elimination is a major excretion pathway and urinary elimination is a minor excretion pathway. Moreover, the 5.38% of the urinary radioactivity was made up of metabolites from a pre-systemic amide hydrolytic pathway and ponatinib itself was not eliminated in urine. Since ponatinib and metabolites are excreted predominantly in faeces, a decreased oral clearance (CL/F) and increased exposure are not anticipated in patients with renal impairment. The sponsor therefore believes a study in renal impaired patients is not necessary.

Response to delegate questions

Delegate question 1

The sponsor is requested to comment as to why there was up to 50% inter-subject variability of both C_{max} and AUC at the 45 mg/day dose.

Sponsor response

In the Phase I trial AP24534-07-101, the steady state geometric mean C_{max} (%CV) and $AUC_{0-\tau}$ (%CV) in CML patients who received daily ponatinib doses of 45 mg were 77.41 (49.9) ng/mL and 1296 (48.1) ng.hr/mL respectively indicating that the variability is

[60] Since 2005, the FDA and European regulators have required that nearly all new molecular entities be evaluated in a Thorough QT (TQT) study to determine a drug's effect on the QT interval. The TQT study serves to assess the potential arrhythmia liability of a drug.

approximately 2 fold in the patient population. The reason for the observed variability of ponatinib PK in patients is not known. However, there is less inter-subject variability in normal volunteers (C_{max} 26% and AUC 29% in the food effect trial AP24534-11-102, N = 24) suggesting the variability observed in patients could be influenced by the clinical setting or other factors. The degree of inter-patient variability observed in patients administered ponatinib is not uncommon for oral TKIs. Gao and colleagues have reported the inter-patient variability (% CV) in AUC of imatinib, nilotinib, erlotinib, sunitinib and sorafenib as 25%, 51.9%, 64%, 41% and 39-82%, respectively.[61] The work done by Undevia and colleagues suggests a number of characteristics that are attributed with the relatively large degree of variability in exposure of anticancer drugs[62] including: disease state, large number of co-medications (poly pharmacy), food, low solubility of the drug, and the pH effect on solubility, and involvement of CYP3A enzymes for metabolism. Based on the literature, most of the parameters above could contribute to the observed variability of ponatinib exposure in patients (except for the effect of gastric pH and food which were studied with ponatinib and found not to have a meaningful effect on PK), and that the observed CV of 50% in AUC is relatively common amongst oral anticancer agents.

Delegate question 2

What proportion of those experiencing an SAE in each of the Phase I, II and III trials resumed ponatinib treatment? Were those experiencing an SAE who were then unable to resume also included as treatment-related discontinuations?

Sponsor response to delegate question 2

The table below shows the proportion of patients who experienced an SAE or treatment-related SAE (RSAE) in the Phase I, II and III trials. The proportion of patients who resumed treatment following their last SAE or RSAE was high and ranged from 78.2 to 94.9% and 91.2 to 93.3% respectively. The proportion of patients with an RSAE leading to treatment-related discontinuation was low across all studies (<10% relative to the # of RSAEs and 1-2% overall).

Table 22: Proportion of patients who experienced an SAE or treatment-related SAE (RSAE) in the Phase I, II and III trials

	Phase 1 (N=81)	Phase 2 (N=449)	Phase 3 (N=153)
Patients with SAE on study treatment, n	55	241	39
Last SAE followed by resumption of treatment, n(%)	43 (78.2)	216 (89.6)	37 (94.9)
Last SAE followed by discontinuation, n(%)	12 (21.8)	25 (10.4)	2 (5.1)
Patients with treatment related SAE (RSAE) on study treatment, n	15	125	26
Last RSAE followed by resumption of treatment, n(%)	14 (93.3)	114 (91.2)	24 (92.3)
Last RSAE followed by discontinuation, n(%)	1 (6.7)	11 (8.8)	2 (7.7)

Delegate question 3

The sponsor is requested to present in a graph, the percentage of patients in Studies 101 and 201 who experienced 1 SAE, 2 SAEs, ≥3 SAEs.

Sponsor response to delegate question 3

The figures below (4 and 5) with the proportion of patients experiencing multiple AEs provides the percentage of patients in Studies 101 and 201 who experienced 1, 2, or 3 or more SAEs, notably 33% and 46% of the CP-CML patients experienced no SAEs in the Phase I and II trials, respectively.

[61] Gao B, Yeap S, Clements A, et al. Evidence for therapeutic drug monitoring of targeted anticancer therapies. J Clin Oncol. 2012 Nov 10;30(32):4017-25.
[62] Undevia SD, Gomez-Abuin G, Ratain MJ. Pharmacokinetic variability of anticancer agents. Nat Rev Cancer. 2005 Jun;5(6):447-58.

Figure 4: Proportion of patients experiencing 0, 1, 2, or 3 or more Serious Adverse Events (SAEs) in Study 101 (n=81)

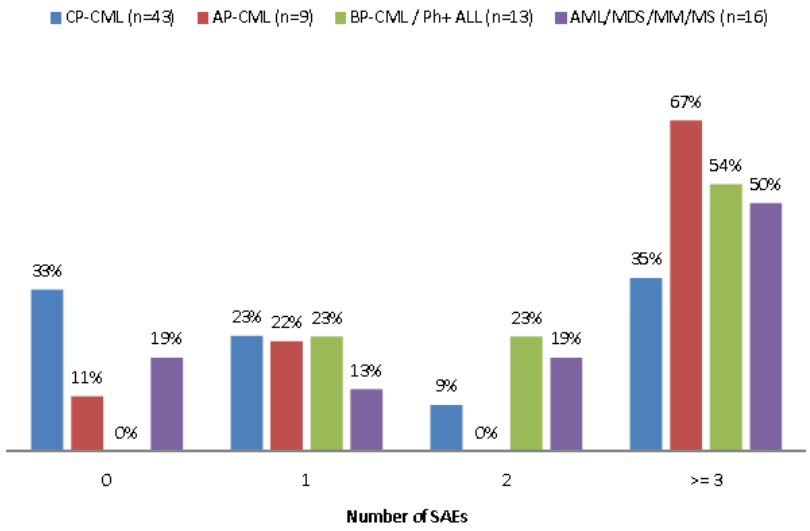
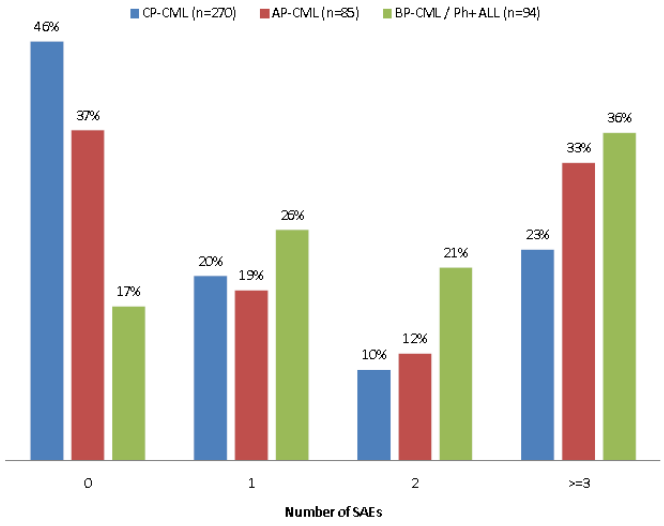


Figure 5: Proportion of patients experiencing 0, 1, 2, or 3 or more Serious Adverse Events (SAEs) in Study 201 (n=449)



Delegate question 4

To clarify the discordance between the figures presented in the Australian PI and the US PI, the sponsor is requested to present the rates of vascular occlusive events (using both the EMA specified terms, in the CER and those thought to be used by the FDA in reaching their figures), with a justification for any that are excluded. This information needs to be included in the PI, including any discrepancies.

Sponsor response to delegate question 4

The sponsor has updated the PI to include the incidence rates of vascular occlusive events, comprising cerebrovascular, cardiovascular and peripheral vascular arterial thrombotic events, and venous events. The vascular occlusive events have been identified using a pre-specified set of more than 400 MedDRA search terms. During the course of the ongoing Article 20 referral procedure in the EU, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has endorsed these terms. Therefore, the vascular occlusive incidence rates in the Australian PI and the draft SmPC being considered by the PRAC are identical. The list of ARIAD's search terms, those terms thought to be used by FDA, and the sponsor's

justifications for the exclusion of any FDA terms were provided in a *Sponsor's comments on foreign PI* (not included here; beyond the scope of this AusPAR).

The sponsor does not agree that a statement in the Australian PI related to potential differences of vascular occlusion preferred terms used in the EU SmPC/Australian PI (which use the same terms) compared to US PI is needed. An Australian specific website will help ensure that Australian healthcare professionals and consumers are provided with Australian specific Iclusig information, thereby minimising potential confusion. References from the Australian PI to other prescribing information (US or EU) would only contribute to or cause confusion. The sponsor is unaware of any Australian PI that references prescribing information in other territories and is unclear why an unprecedented action is needed in the case of Iclusig.

Delegate question 5

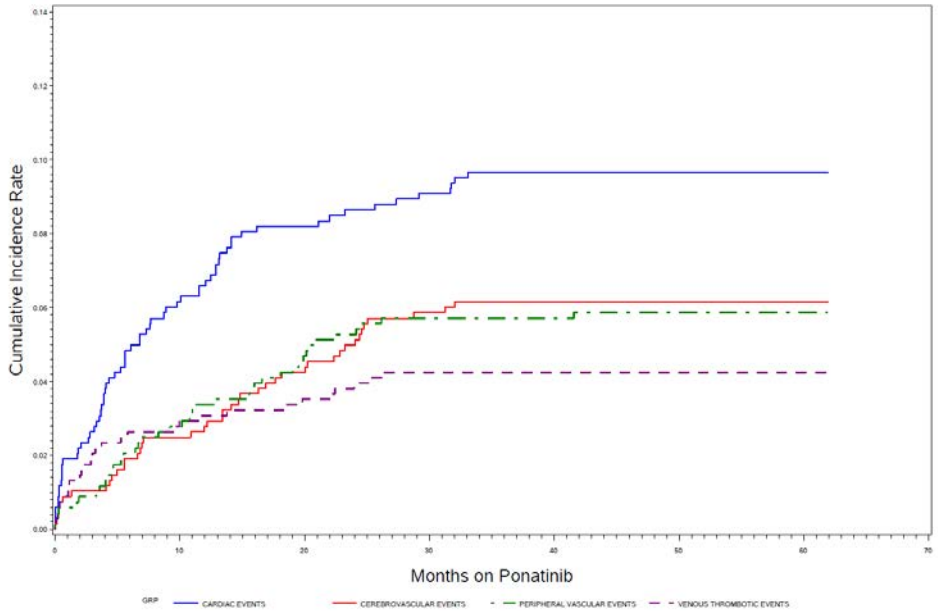
In order to capture the cumulative risk for adverse vascular occlusive events, the sponsor is requested to present data as a graph from the table Incidence rate of AEs by time of initial onset for all patients treated with ponatinib, Integrated safety summary, cut-off January 6, 2014) using the collated MedDRA terms for vascular events as requested by the EMA plus any additional terms the sponsor considers the FDA used, in the pre ACPM response and incorporate these into the PI. It is noted that this table only addresses first events.

Sponsor response to delegate question 5

The requested figure is attached (see 'Figure 6). However, as noted in the response 'in the section addressing the vascular occlusive section of the PI, the sponsor feels the inclusion of this figure won't contribute meaningfully to the understanding of the physician and could be confusing.

Thus, it has not been included in the PI.

Figure 6: Cumulative incidence rates of vascular occlusive adverse events. All patients treated with ponatinib in Studies AP24534-07-101, AP24534-10-201, AP24534-12-301 (N=683)



Delegate question 6

The sponsor indicated that the liver necropsy report was pending for the case of severe DILI in the Japanese Phase I/II studies in Ph+ ALL discussed in the second round

evaluation. The sponsor is requested to provide the result of this in the pre-ACPM summary.

Sponsor response to delegate question 6

The case referenced relates to one patient and an updated case summary that includes the liver necropsy report is appended.

Delegate question 7

The sponsor is requested to comment as to why so few cases of hypertension were considered treatment-related in Study 201.

Sponsor response to delegate question 7

The assessments of the causal relationship of Iclusig to the adverse events observed in the 201 study were made by the Investigators based on their medical judgment and according to the criteria set forth in the protocol. All treatment related adverse events reported by the sponsor have relied on this causality assessment. In the 201 study, after a minimum of 27 months of follow-up on all patients treatment-emergent hypertension was reported in 26% of patients (2% serious), with 13% (56/449) experiencing hypertension assessed by the investigator as treatment related. One factor that likely contributed to the investigator's causality assessment was the baseline history of hypertension in the 201 study population (77% [346/449] had a Grade 1 hypertension). Additionally, many of the observations of hypertension and elevations in blood pressure observed in the trial were transient, which could have called into question the contribution of Iclusig for the investigator.

Delegate question 8

The sponsor is requested to explain whether the figures for discontinuations due to AEs in Study 101 and 201 reported in the PI are from the 120-day cut-off, and if so, to update these and include in the PI in the adverse events section.

Sponsor response to delegate question 8

The figures for discontinuations due to AEs have been updated.

Risk management plan

The sponsor's replies to the comments in the RMP Assessment Report received on 9 September 2014 were provided. The sponsor has agreed to implement a patient card as suggested by the Delegate. A revised ASA will be prepared and submitted before approval, after the labelling negotiations have concluded.

Advisory Committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Iclusig, film-coated tablets, containing 15 mg and 45 mg of the new chemical entity, ponatinib hydrochloride, to have an overall positive benefit–risk profile for the amended indication**:**

Iclusig (ponatinib) is indicated for the treatment of adult patients with:

- *Chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) with intolerance of, or disease resistant to, at least two prior tyrosine kinase inhibitors (TKI's), or where there is a T315I mutation*

– *Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) whose disease is resistant to, or who are intolerant of, imatinib and dasatinib, or where there is a T315I mutation.*

Therapy should be initiated and monitored by a haematologist with expertise in managing adult leukaemia.

In making this recommendation the ACPM advised that a statement regarding treatment by a haematologist would ensure that this product was prescribed by experienced clinicians familiar with prescribing tyrosine kinase inhibitors and aware of their toxicity. The ACPM noted that most patients would be under the supervision of a haematologist at this stage of their disease.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Inclusion of a boxed warning to alert prescribers and patients of the risks of vascular occlusion and cardiac failure only. The ACPM advised that a boxed warning regarding hepatoxicity was not necessary at this point.
- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- Under Hepatoxicity, include the statement regarding monitoring for liver function tests similar to that used in the US PI, 'Monitor liver function tests at baseline, then at least monthly or as clinically indicated. Interrupt, reduce or discontinue Iclusig as clinically indicated'.
- In addition, under Hepatoxicity, include a warning about the potential for severe drug induced liver injury.
- Under Dosage and Administration, the addition of the words **'**Although late responses may be observed…**'** to '…Consider discontinuing ponatinib if a haematologic response has not occurred by 3 months (90 days) especially in subjects at risk of vascular adverse event…', as some patients with CML responded to treatment with ponatinib after more than 90 days of treatment.
- Under Dose Adjustments or Modifications, change the heading Pancreatitis and Serum Lipase to Pancreatitis and /or Elevated Serum Lipase, to reflect the reason for the dose adjustment.
- Under Overdosage, add information similar to the overdosage information contained in the US PI as it provides more specific information for the clinician.
- Consider the addition of the information under Patient Counselling Information in the US PI as this could be very useful for clinicians.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. Whether the incidence of vascular occlusive adverse events and cardiac failure merit a boxed warning and whether hepatotoxicity should be included in the boxed warning.

   The ACPM advised that a black box warning should be included for vascular events and cardiac failure, given the adverse events rates reported thus far.

   Regarding hepatoxicity, the ACPM noted that the US PI reported a case of fulminant hepatic failure leading to death within one week of starting Iclusig and two additional fatal cases of acute liver failure. The ACPM also noted one Japanese fatality and the necropsy report provided by the sponsor. In the pooled safety analysis of the clincial trials, the ACPM noted that hepatoxicity was relatively common (27.2%), few patients had treatment discontinued due to hepatic adverse events (0.4%) and there were no fatal adverse events and no reports of liver failure.

   Taking this into consideration, the ACPM advised that a black box warning for hepatoxicity is not necessary at this point. However, the ACPM advised there should be recommendations in the PI regarding the need for monitoring potential liver toxicity as well as a warning about the potential for severe drug induced liver injury.

2. Whether the sponsor should be required to develop a patient information card to alert health care professionals (especially in emergency setting) of the side effects of ponatinib.

   The ACPM advised that the development of a patient information card should be required, particularly to alert health professionals in the emergency setting about the severe side effects of ponatinib. The ACPM noted that ACSOM also advised than an alert card is appropriate.

3. Whether the sponsor's updated information about the vascular occlusive/cardiovascular risks in the pre-ACPM response is considered acceptable for inclusion in the Australian PI (compared to US data).

   The ACPM noted the rate of vascular occlusive/cardiovascular events was high; however, this probably would not unduly influence the prescriber's choice of drug. The ACPM also noted that there was discrepancy between the adverse event rates in the US PI and the Australian PI due to the description and classification of adverse events. The ACPM considered that there should ideally be consistency in the information presented in the PIs.

4. Whether the sponsor should be required as a condition of registration, to perform a Thorough QT study meeting the ICH/EMA Guidelines.

   The ACPM noted that subjects at risk were excluded from the clinical trials (baseline prolonged QT, taking drugs known to have effect on QT interval and those in cardiac failure). However, the ACPM considered that there was no strong signal from the trials to warrant a dedicated QT interval study. The ACPM advised that to reduce the risk of such events occurring a baseline study for QT interval should be performed as well as careful patient selection (where possible) on the basis of risk factor analysis for diabetes mellitus, heart disease, ischaemia, hypertension and smoking. Post market surveillance will also be useful to detect any signals for QT prolongation.

5. The inclusion of the statement in the indication that states there is no overall survival or proven improvement in symptoms.

   The ACPM advised that the indication should not include a statement that there is no overall survival or proven improvement in symptoms as the median duration of response has not yet been determined.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Iclusig ponatinib (as hydrochloride) 15 mg and 45 mg film-coated tablet bottles for oral administration, indicated for:

> *Iclusig is indicated for the treatment of adult patients with:*
>
> 1. *Chronic phase, accelerated phase, or blast phase chronic myeloid Ieukaemia whose disease is resistant to, or who are intolerant of at least two prior tyrosine kinase inhibitors; or where there is a T315I mutation.*
> 2. *Philadelphia chromosome-positive acute lymphoblastic Ieukaemia (Ph+ ALL) whose disease is resistant to, or who are intoIerant of dasatinib and for whom subsequent treatment with imatinib is not clinicalIy appropriate; or where there is a T315I mutation.*
>
> *Therapy with Iclusig should be initiated and monitored by a haematologist with expertise in managing adult leukaemias.*

Specific conditions of registration applying to these goods

1. Implementation of the EU Risk Management Plan (RMP), version 9.0, dated June 2014, data lock point 6 January2014, with Australian Specific Annex (subsequent to version 2.0), to be revised to the satisfaction of the TGA.
2. The development of a patient information card for patients to carry to alert healthcare professionals about the potential side effects of ponatinib Inclusion of a boxed warning to alert prescribers and patients of the risks of vascular occlusion and cardiac failure.
3. Submission of the following clinical trial(s) as Category I submissions within 6 months of completion:
    a. Study 107 examining the effect of rifampicin on the pharmacokinetics of ponatinib
    b. Study 108 examining the effect of Iansoprazole on the pharmacokinetics of ponatinib

Attachment 1. Product Information

The Product Information approved for main Iclusig at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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