24 September 2015
EMA/671413/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Iclusig

International non-proprietary name: ponatinib

Procedure No. EMEA/H/C/002695/X/0023

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

λ = terminal phase rate constant

ABL = c-abl proto-oncogene

AE = adverse event

AUC0-∞ = area under the plasma concentration vs time curve from time 0 to infinity

AUC0-t = area under the plasma concentration vs time curve from time 0 to the time of the last quantifiable concentration

BMI = body mass index

CI = confidence interval

CL/F = apparent oral clearance

Cmax = maximum observed plasma concentration

CML = chronic myeloid leukemia

CQA Critical Quality Attribute

CRU = clinical research unit

CV = coefficient of variation

EC European Commission

GCP = Good Clinical Practice

HCl = hydrochloric acid

HDPE High Density Polyethylene

HPLC High performance liquid chromatography

ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

KF Karl Fisher titration

LDPE Low density polyethylene

LSM = least-squares mean

Ph. Eur. European Pharmacopoeia

PK = pharmacokinetic(s)

QTPP Quality target product profile

RH Relative Humidity

SAE = serious adverse event

SAP = statistical analysis plan

SD = standard deviation

SmPC Summary of Product Characteristics

SOP = standard operating procedure

t½ = terminal elimination half-life

TEAE = treatment-emergent adverse event

Tmax = time to maximum observed plasma concentration

TSE Transmissible Spongiform Encephalopathy

V/F = apparent volume of distribution

UV Ultraviolet

WBC = white blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant ARIAD Pharma Ltd submitted on 05 May 2015 an application for extension of a Marketing Authorisation to the European Medicines Agency (EMA) for Iclusig. The MAH applied for a new strength: 30 mg film coated tablets.

Iclusig, was designated as an orphan medicinal product EU/3/09/715 and EU/3/09/716 on 02/02/2010..

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008, Annex I 2.(c) Change or addition of a new strength/potency.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

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

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Rafe Survana

Assessors: Keith Pugh, Henry Stemplewski, Benoy Daniel, Julia Double

- The application was received by the EMA on 05 May 2015.
- The procedure started on 28 May 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 06 August 2015
- During the meeting on 24 September, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation for a new strength Iclusig 30 mg film-coated tablets.
- The CHMP adopted a report on similarity of Iclusig on 24 September 2015

2. Scientific discussion

2.1. Introduction

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

The Marketing Authorisation was granted by the European Commission on 1 July 2013 for the following indications in adult patients: (a) 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 and (b) Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation.

Ponatinib is currently available in the EU as 15 mg and 45 mg tablet strengths. These two strengths are of the same composition and are dose-weight proportional.

The applicant submitted an application for extension of a Marketing Authorisation for Iclusig 30 mg film coated tablets. The results of the bioequivalence study AP24534-14-112, that evaluated the bioequivalence of two 15 mg tablets of ponatinib compared to a single 30 mg tablet, has been submitted to support this application.

The currently approved product information recommends a starting dose of 45 mg of ponatinib once daily. Dose modifications (to 30 mg or 15 mg) or interruption of dosing should be considered for the management of haematological and non-haematological toxicities (see SmPC section 4.2). In addition dose reduction may be considered in patients with chronic phase (CP) chronic myeloid leukaemia (CML) who have achieved Major Cytogenetic Response. In order to achieve a 30 mg dose, patients currently take two 15 mg tablets; therefore the 30 mg tablet strength has been developed to improve patient convenience by reducing the number of tablets per dose. The addition of this strength is expected to simplify handling of the tablets by the patient and the administration of ponatinib. As the use of multiple dose units to achieve a single dose may increase medication errors, the addition of the 30 mg strength is therefore expected to reduce the probability of medication error by limiting the daily intake to one single tablet for a 30 mg daily dose.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 30 mg of ponatinib as active substance.

Other ingredients are:

Tablet core: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal anhydrous silica and magnesium stearate.

Tablet coating: talc, macrogol 4000, poly(vinyl alcohol) and titanium dioxide (E171).

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

2.2.2. Active Substance

The active substance used to manufacture Iclusig 30 mg film-coated tablets is the same as that employed for the manufacture of the approved Iclusig 15 mg and 45 mg film-coated tablets. Therefore, no information on the active substance has been submitted or assessed within this line extension application.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Iclusig is currently available in the EU in two strengths: 15 mg and 45 mg immediate release film-coated tablets. The aim of this line extension application was to develop an additional 30 mg strength of ponatinib immediate release film-coated tablets in order to improve patient convenience and simplify handling when a 30 mg dose of ponatinib is required.

The quality target product profile (QTPP) for this product was defined in line with the approved strengths as: 30 mg immediate release film-coated tablets, which are orally bioavailable and allow a once daily administration, have a 24 or longer shelf-life, meet appropriate quality criteria and are packaged in a bottle configuration sufficiently protective so as to assure the product quality throughout its shelf-life. The critical quality attributes (CQAs) identified were: description, identification, assay, degradation products, content uniformity, water content and dissolution.

As the 30 mg tablets represent an intermediate strength to those already approved, the MAH applied the same approach used for the already approved strengths to this new strength. All excipients selected are those already used in the already-approved tablets and there are no novel excipients used in the 30 mg formulation. The list of excipients is included in section 6.1 of the SmPC and in section 2.2.1 of this report. They are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with the exception of Opadry II film-coating system. Opadry II is a commonly used film-coating system which is manufactured using four compendial excipients: talc, Macrogol 4000, polyvinyl alcohol, and titanium dioxide (E171).

The manufacturing process is also analogous, using a common blend and a single direct compression tabletting method, resulting in a tablet core composition proportional to the 15 and 45 mg tablets. All tablet strengths are white, film-coated, but have different sizes and have different markings to allow differentiation.

As differences in pharmacokinetic behaviour were not expected, a single dose clinical study was conducted in order to assess the bioequivalence of a single 30 mg tablet to two 15 mg tablets in healthy adult subjects using standard bioequivalence criteria (see clinical section). Following this bioequivalence study, an *in vitro* dissolution study was conducted to compare the dissolution profile of the three registration batches (composite profile) and the commercial scale batch using the dissolution method registered for the 15 and 45 mg strengths which had previously been shown to be discriminatory. The profiles were shown to be similar based on calculation of f_2 similarity factors and the differences did not impact on *in vivo* performance.

The batch size of the 30 mg tablets used in the bioequivalence study was representative of commercial scale. Nonetheless, the applicant has committed to carry out comparative dissolution studieson at least for the next two commercial scale batches of the 30 mg strength.

The primary packaging consists of HDPE bottles with screw-top closures, containing 30 film-coated tablets, together with one plastic canister containing molecular sieve desiccant. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

As for the 15 mg and 45 mg strengths, Iclusig 30 mg tablets are manufactured using a direct compression process which comprises three steps: blending, compression and film-coating. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. Since the manufacturing process is the same for all strengths, and the applied strength lies within the range of the approved strengths, the validation strategy for the 30 mg tablets employed a bracketing approach. Data from three commercial scale batches of the 15 mg tablets and 45 mg tablets (lower and upper ends of commercially available strengths) and one commercial scale batch of the 30 mg tablets manufactured at the same site were provided. These data demonstrate that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of dosage form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form. It includes test for description (visual), identity (HPLC, UV), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.) and water content (KF). The proposed specification is in line with that approved for the 15 mg and 45 mg strengths. The finished product is released to market based on the release specifications, through traditional final product release testing

The analytical methods used are those already registered for the 15 mg and 45 mg strengths. They have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis results from three pilot scale and one commercial scale batches of Iclusig 30 mg tablets have been provided confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Since the 15 mg and 45 mg tablets represent the extremes of the ponatinib dose strength range and the 30 mg tablet uses a common granulate and is dose-proportional to the approved presentations, a bracketing approach was selected for the stability studies on the intermediate 30 mg strength. Stability data on three pilot scale batches of 30 mg tablets and three commercial scale batches each of 15 mg and 45 mg tablets manufactured at the same site and stored under long term conditions for up to 9 months at 25 ºC / 60% RH, up to 9 months under intermediate conditions at 30 ºC / 75% RH, and for up to 6 months under accelerated conditions at 40 ºC / 75% RH, according to the ICH guidelines, were provided. All batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

In addition, supportive stability data from four pilot scale and three commercial scale batches of 15 mg tablets, and seven commercial scale batches of 45 mg tablets, manufactured at an alternative site (not used for the manufacture of the 30 mg tablets), stored for up 24 months at long term conditions and up to 6 months under accelerated conditions, were provided.

Samples were tested for description, water content, dissolution, assay and impurities. The analytical procedures used are stability indicating.

All the results presented are within specification at all time-points. Stability data currently available for the 30 mg tablets demonstrate equivalent performance to the approved strengths when stored in the proposed commercial packaging configuration. Taken together, the totality of stability data demonstrates the comparability of all lots across all strengths and manufacturing sites.

In addition, a bulk hold study was conducted for all strengths produced at the proposed manufacturing site for the 30 mg tablets. One batch of each strength was stored for 12 months at controlled room temperature (20-25 ºC) inside two LDPE bags, in between which two bags of desiccant were placed. The LDPE bags were closed with cable tie and stored within a HDPE container. Samples were tested for description, water content, dissolution, assay, impurities, microbial enumeration. All the results presented met the defined specifications at all time-points.

Moreover, one batch of 15 mg tablets and two batches of 45 mg tablets were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. These batches were manufactured at an alternative site not used for the manufacture of the 30 mg tablets, but given the data above, can be considered representative of batches manufactured at all sites. Samples were tested for description, assay and dissolution before and after light exposure. Although a colour change from white to light yellow was observed in tablets directly exposed to light, tablets stored in the proposed commercial HDPE bottles met all specificationsBased on available stability data, the currently approved shelf-life for 15 mg and 45 mg tablets in the proposed packaging configuration of 2 years with a storage precaution of “store in the original container in order to protect from light” as stated in the SmPC is equally applicable to the 30 mg tablets.

Adventitious agents

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

All other components used in the formulation are of vegetable or synthetic origin and do not contain any material of bovine, ovine or caprine derivation.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. Since the 30 mg tablets represent an intermediate strength to those already authorised, and the three strengths are prepared using a common granulate and the same manufacturing process, a bracketing approach has been followed to conduct the process validation and stability studies. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in

turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

N/A

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

2.4.2. Pharmacokinetics

The applicant has submitted the results of the Study AP24534-14-112: A single dose bioequivalence study comparing a 30 mg tablet with two 15 mg tablets of ponatinib in healthy adult subjects. This study investigated the relative bioavailability of a single 30 mg ponatinib tablet versus that of two 15 mg ponatinib tablets, using standard bioequivalence criteria.

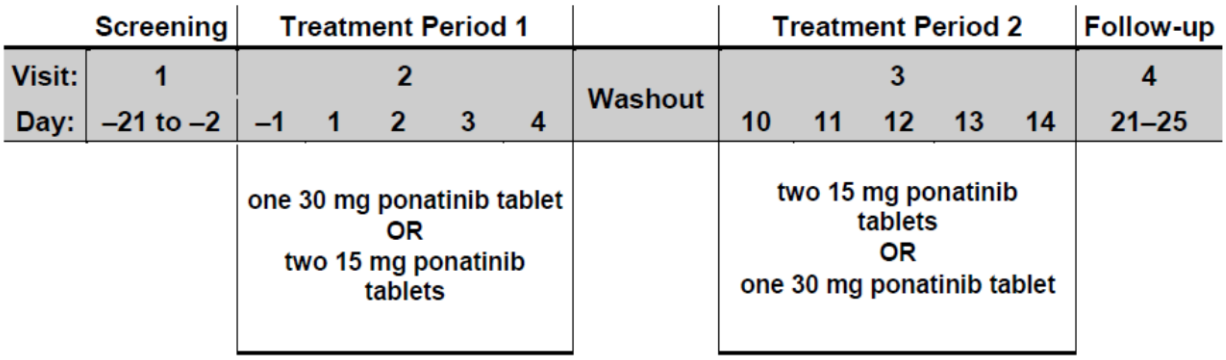
The proposed 30 mg tablet strength is proportional in dose and weight to the 15 mg and 45 mg tablets.

The study was conducted between 07/07/2014 and 09/08/2014 at INC Research Toronto, Canada. The bioanalytical facility for the study was at Quintiles, New York.

The primary objective was to determine whether a single dose of a 30 mg ponatinib tablet was bioequivalent to two 15 mg ponatinib tablets in healthy subjects using standard bioequivalence criteria. The secondary objective was to obtain additional safety and tolerability data on ponatinib in healthy subjects.

The study was conducted as an open-label, randomized, 2-period, crossover study in healthy subjects. The study consisted of 2 treatment periods separated by a washout period of at least 10 days between ponatinib doses. In each treatment period, subjects received either a single oral dose of 30 mg ponatinib tablet or two 15 mg ponatinib tablets, in randomized order.

Figure 1 Study Design



Healthy male and female subjects 18 to 55 years of age, inclusive, were selected to participate in this study. Approximately 34 healthy subjects were planned to be enrolled for this study, with the intent to ensure evaluable data from at least 31 subjects. A total of 67 subjects were screened for this study. Of these, 46 subjects were eligible to proceed to the treatment phase. The most common reasons for screening failure were exclusion criterion #2 (clinically significant vital signs or laboratory values) and inclusion criterion #2 (BMI out of range).

In total, 36 subjects were randomized to the treatment phase. Of these subjects, 32 (88.9%) completed the study.

Table 1: Summary of Subject Each subject participated in the study for approximately 6 weeks. Participation included a screening visit within 21 days before administration of the study drug and two 5-day (4-night) inpatient stays separated by at least 10 days between study drug administrations. Subjects returned for a safety follow-up visit within 10 to 14 days of the last study drug administration. Subjects were admitted to the clinical research unit (CRU) on Day –1 of each treatment period. On Day 1, subjects received a single oral dose of ponatinib. Subjects remained in the CRU until the morning of Day 4 for completion of PK sampling at 72 hours. The end of the study was defined as the last visit of the last subject.

Subjects were randomly assigned to 1 of 2 treatment sequences (i.e., AB or BA):

- Treatment A: one 30 mg ponatinib tablet
- Treatment B: two 15 mg ponatinib tablets

All study drugs were administered in the morning following a 10-hour fast with 240 mL of ambient drinking water. Subjects received the study drugs at approximately the same time on each dosing day (±15 minutes). For Treatment B, both 15 mg tablets were taken within 5 minutes.

Ponatinib 15 mg and 30 mg oral tablets were supplied by ARIAD Pharmaceuticals, Inc. in white high-density polyethylene bottles with child-resistant caps with liner. Ponatinib for investigational use was supplied as small, round, white, film-coated, biconvex tablets. The 15 mg tablets were marked with A5 on one side and no markings on the other side; the 30 mg tablets were marked with C7 on one side and no markings on the other side.

Pharmacokinetic Assessments

During each treatment period, venous blood samples were collected to determine the plasma concentrations of ponatinib. Samples were collected, processed, and shipped according to the site's Standard Operating Procedures (SOPs) and instructions from the sponsor or bioanalytical laboratory. In each treatment phase, a total of 15 blood samples (5 mL each) were collected at pre-dose, 0.5, 1.00, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 18.00, 24.00, 36.00, 48.00, 60.00 and 72.00 hours post dose.

The plasma samples were analysed by Quintiles BioSciences, Inc. using a validated LC-MS/MS analytical method. The calibration range was from 0.5 to 250 ng/mL (a 5-fold dilution was validated, extending the range to 1250 ng/mL).

Plasma samples were shipped frozen on dry ice from the research site to Quintiles BioSciences, Inc.

The plasma PK parameters for ponatinib included the following:

- Cmax: Maximum observed plasma concentration; identified from all available concentration values at recorded time points
- Tmax: Time to maximum observed plasma concentration; if the same Cmax was recorded more than once during the treatment period, the earliest occurrence was considered the Tmax
- AUC0-t: Area under the plasma concentration vs time curve from time 0 to the time of the last quantifiable concentration; calculated by the log-linear trapezoidal rule using actual times relative to dosing (not planned sampling times)
- AUC0-∞: Area under the plasma concentration vs time curve from time 0 to infinity; calculated as AUC0-t + Clast / λ, where Clast is the last measureable drug concentration
- t½: Terminal elimination half-life; calculated as ln(2) / λ
- λ: Terminal phase rate constant
- CL/F: Apparent oral clearance; calculated by the quotient of dose / AUC0-∞
- V/F: Apparent volume of distribution; calculated as dose / (λ × AUC0-∞)

The AUC extrapolation to infinity must have been ≤20% of the total area for AUC0-∞ to be considered reliable. Parameters such as t½, λ, CL/F, and V/F were flagged for subjects with an unreliable AUC0-∞.

For each of the parameters, the null hypothesis was that there is a treatment effect, and the alternative hypothesis was that there is no treatment effect. For each of the contrasts or pairwise comparisons, the null hypothesis was that there was a treatment effect difference between the tested pair, and the alternative hypothesis was that there was no treatment effect difference between the tested pair.

The two 1-sided tests were as follows, where *T* was the test (one 30 mg tablet) and *R* was the reference (two 15 mg tablets):

- H01: $\mu T/\mu R \leq 80\%$ vs HA1: $\mu T/\mu R > 80\%$ and
- H02: $\mu T/\mu R \geq 125\%$ vs HA2: $\mu T/\mu R < 125\%$

The significance level for each 1-sided test was controlled at 0.05. A 5% Type-I error rate with a p-value less than 0.05 was considered statistically significant for all individual hypothesis tests. All statistical tests were performed using 2-tailed significance criteria.

Analysis of ln-transformed PK endpoints (Cmax, AUC0-t, and AUC0-∞) for ponatinib was performed using a mixed-effect model. The model included treatment sequence, period, and treatment as fixed effects and subject nested within treatment sequence as a random effect.

The least squares mean (LSM), the difference between treatment LSM, and the standard error associated with the difference were calculated for each PK endpoint. Residual, subject nested within sequence, and inter-subject variance, along with the intra-subject and inter-subject coefficient of variation (CV), was reported. Ratios of LSM were calculated using the exponential of the difference between treatment LSM from the analyses on the ln-transformed Cmax, AUC0-t, and AUC0-∞. Bioequivalence was concluded if the 90% confidence interval (CI) for the ratio of population geometric means of Cmax, AUC0-t, and AUC0-∞ between the 2 treatments were within the equivalence limits of 80% to 125%.

Tmax was not transformed and was analysed using non-parametric analysis (Walsh averages and appropriate quartile of the Wilcoxon signed rank test statistic). Median and range for each treatment and p-value were presented.

Results

Descriptive statistics of the derived PK parameters for ponatinib are presented by in the Table 3 below.

Table 2: Statistics of the derived PK parameters for ponatinib

Treatment	Summary Statistic	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (h*ng/mL)	$AUC_{0-\infty}$ (h*ng/mL)	$t_{1/2}$ (h)	CL/F (L/h)	V/F (L)
Two 15 mg	Mean	34.60	–	791.6	892.9	23.78	37.83	1291
tablets (N=32[a])	SD	8.9097	–	242.46	296.56	4.7148	13.895	548.50
	CV (%)	25.8	–	30.6	33.2	19.8	36.7	42.5
	Min	17.5	4.0	399	432	14.1	20.6	632
	Median	33.55	6.00	832.9	883.9	24.50	33.94	1172
	Max	53.9	12.0	1228	1455	33.2	69.5	2727
	Geo Mean	33.49	–	753.1	843.2	–	35.58	1196
	Geo CV (%)	26.6	–	33.8	36.4	–	36.4	40.2
	Q1	–	6.00	–	–	–	–	–
	Q3	–	8.00	–	–	–	–	–
One 30 mg	Mean	35.36	–	790.4	877.4	23.48	38.31	1270
tablet (N=32[a])	SD	8.6867	–	237.04	281.02	4.2855	14.274	466.52
	CV (%)	24.6	–	30.0	32.0	18.3	37.3	36.7
	Min	18.5	6.0	380	430	15.9	20.7	732
	Median	34.40	6.00	772.3	879.8	24.25	34.10	1091
	Max	52.7	8.0	1223	1450	32.5	69.8	2570
	Geo Mean	34.25	–	752.9	831.4	–	36.08	1201
	Geo CV (%)	26.7	–	33.6	35.5	–	35.5	33.7
	Q1	–	6.00	–	–	–	–	–
	Q3	–	6.00	–	–	–	–	–

CV=coefficient of variation; Geo=geometric; Min=minimum observed value; Max=maximum observed value; Q1=first quartile; Q3=third quartile; SD=standard deviation

[a] n=28 for AUC0-∞, t1/2, CL/F, and V/F because 4 subjects did not have reliable AUC0-∞ values for both treatments.

Mean ponatinib plasma concentrations reached a maximum at approximately 6 hours after intake of both treatments with 30 mg ponatinib (either as two 15 mg tablets or one 30 mg tablet). PK parameters for both treatments were similar. All subjects had quantifiable ponatinib plasma concentrations up to the final sampling point at 72 hours post dose for both treatments. The maximum mean concentration reached was similar after both treatments; the ponatinib terminal elimination was the same for the two treatments. The figure below presents the mean (±SD) ponatinib plasma concentration curves over time for the two treatments on linear (top panel) and log-linear (bottom panel) scales.

Figure 2: Mean (±SD) Ponatinib Plasma Concentration Curves (ng/mL) – PK Population

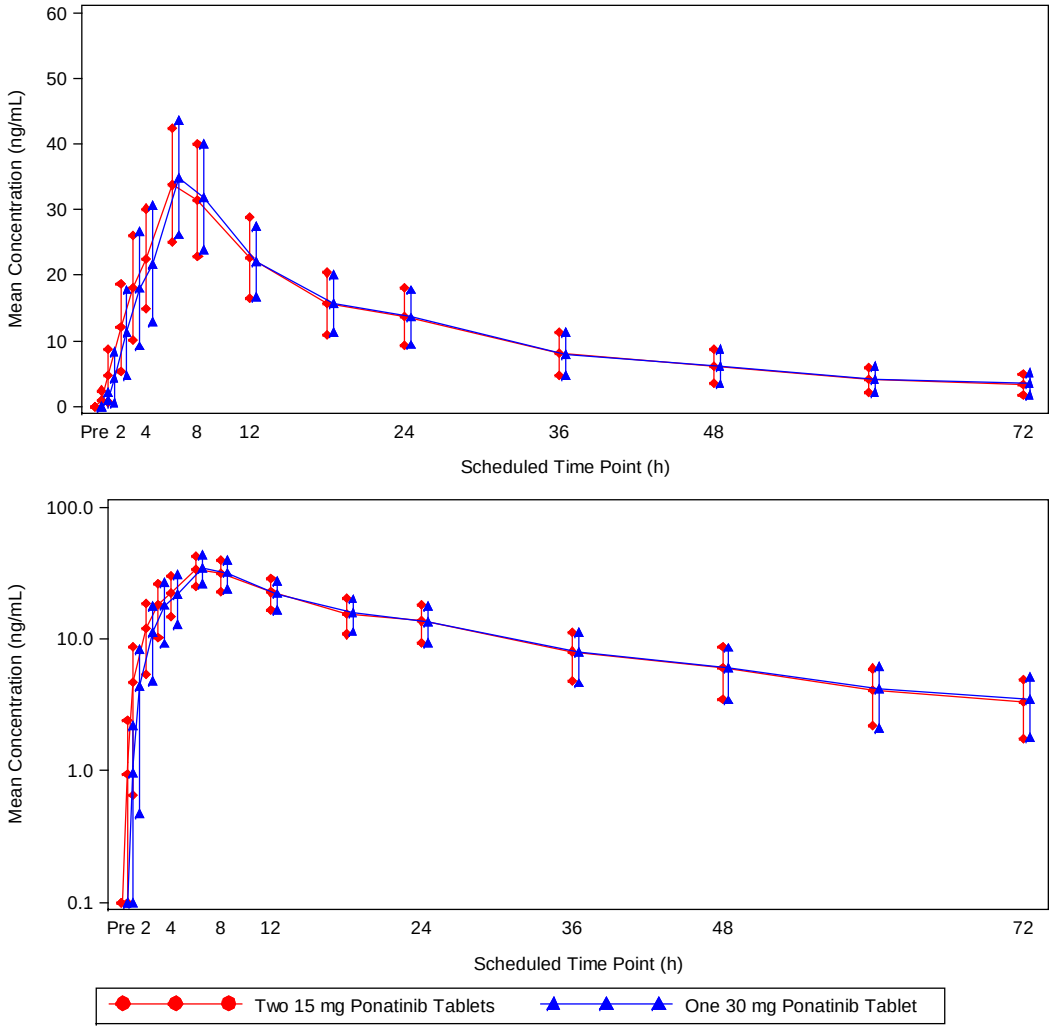


Table 3: Pharmacokinetic parameters for Ponatinib (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng*/ml/h	$AUC_{0-\infty}$ ng*/ml/h	C_{max} ng/ml	t_{max} h
Test (one Iclusig 30 mg tablet)	790.4 ± 237.04	877.4 ± 281.02	35.36 ± 8.6867	6.0 (6.0, 8.0)
Reference (2 tablets of Iclusig 15 mg)	791.6 ± 242.46	892.9 ± 296.56	34.60 ± 8.9097	6.0 (4.0, 12.0)
***Ratio (90% CI)**	100.398 (97.483, 103.400)	99.604 (95.966, 103.381)	102.326 (98.143, 106.686)	

AUC0-t Area under the plasma concentration curve from administration to last observed concentration at time t
Cmax Maximum plasma concentration
tmax Time until Cmax is reached

**In-transformed values*

2.4.3. Pharmacodynamics

N/A

2.4.4. Discussion on clinical pharmacology

The study design of trial AP24534-14-112 is acceptable. The washout period of 10 days is adequate for the crossover design of the study, considering the half-life of the ponatinib (studied at the 45 mg dose) to be 22 hours. The sampling regimen also appears adequate, with sufficiently frequent sampling around the period of expected Tmax and sufficiently long period of sampling (72 hours). The pharmacokinetic variables are adequate for assessment of bioequivalence. There were no major protocol deviations/violations.

No pre-dose levels were detected in any subjects in either period in the pharmacokinetic analyses (data not shown). None of the subjects showed a tmax value in the first sample time. Cmax detected in all subjects were within the validated range.

For 4 subjects, selected PK parameters were excluded from the summary statistics and bioequivalence analysis because the extrapolated area from the last sampling time until infinity used to estimate AUC0-∞ covered more than 20% of the area (i.e., AUC0-t was less than 80% of AUC0-∞). As per the SAP, the values for AUC0-∞, t½, λ, CL/F, and V/F for these subjects were excluded from the summary statistics and statistical analysis.

The estimated geometric mean ratio for Cmax was 102.3%; the 90% confidence intervals (CI) were 98.1% and 106.7%, lower and upper respectively. The estimated geometric mean ratio for AUC0-t was 100.4% and the 90% confidence intervals were 97.5% and 103.4%, lower and upper respectively. The estimated geometric mean ratio for AUC0-∞ was 99.6% and the 90% confidence intervals were 96.0% and 103.4%, lower and upper respectively. Bioequivalence of one 30 mg and two 15 mg ponatinib tablets was concluded since the 90% confidence interval (CI) of the estimated mean ratio of all 3 parameters of Cmax, AUC0-t, and AUC0-∞, fell entirely within the 80% to 125% margins required to conclude bioequivalence of the two treatments.

2.4.5. Conclusions on clinical pharmacology

Study AP24534-14-112 determined that the two treatments of 30 mg ponatinib administered as either one 30 mg tablet or two 15 mg tablets are bioequivalent.

2.5. Clinical efficacy

N/A

2.6. Clinical safety

The safety population in AP24534-14-112 included all 36 healthy adult subjects in the randomized population. A total of 32 subjects in the safety population completed both treatment periods and were exposed to 2 single doses of 30 mg ponatinib (i.e., total exposure 60 mg ponatinib). Four subjects were withdrawn from the study and did not participate in treatment period 2; they were exposed to a single 30 mg dose of ponatinib. One subject was withdrawn from study AP24534-14-112 due to emesis within 10 hours of drug ingestion (two 15 mg tablets), and 2 subjects were withdrawn due to TEAEs: 1 AE of prostatitis, considered unlikely related to the study drug (two 15 mg tablets), and 1 AE of chest pain, considered possibly related to the study drug (one 30 mg tablet).

All TEAEs reported in study AP24534-14-112 were mild or moderate in intensity, and most were considered related to study treatment. The overall incidence of TEAEs was higher with the two 15 mg tablets of ponatinib than with the single 30 mg tablet; 14 subjects (40.0%) experienced 27 TEAEs and 9 subjects (27.3%) experienced 15 TEAEs following the administration of the 15 mg tablets and 30 mg tablet, respectively. The most common TEAE was headache, occurring in 6 subjects (17.1%) after the two 15 mg tablets and in 2 subjects (6.1%) after the single 30 mg tablet. The TEAE of lipase increased occurred in 2 subjects (5.7%) and 3 subjects (9.1%) following administration of two 15 mg tablets and one 30 mg tablet, respectively. All other TEAEs occurred in only 1 or 2 subjects per treatment. All reported TEAEs were resolved at the end of the study. No new type of adverse event was reported in this study which had not been previously reported with ponatinib. Overall, all adverse events reported in this study were consistent with the known safety profile of ponatinib.

No serious adverse events or deaths were reported. No new safety concerns were highlighted in the study from single doses of 30 mg ponatinib, administered as either on 30 mg tablet or two 15 mg tablets.

2.6.1. Discussion and conclusions on clinical safety

Overall, the safety profile observed in AP24534 14 112 was consistent with the known safety profile of ponatinib.

2.7. Risk Management Plan

The currently approved RMP (version 11.2 dated 27 February 2015) was agreed in the framework of variation EMEA/H/C/002695/II/0017 (CHMP opinion issued 26 March 2015). A subsequent version (12.0 dated 8 June 2015) has been assessed in the framework of PSUR 3.

The current RMP refers to the two different strengths of ponatinib currently available (15 mg and 45 mg).

Medication error is not identified as a safety concern in the current RMP.

The MAH did not submit a Risk Management Plan (RMP) as part of the variation application to register a 30 mg tablet for ponatinib. The CHMP agreed with the MAH's proposal that the new 30 mg strength has a minor impact on the RMP and therefore the RMP will be updated with the new information at the next planned update which is foreseen by the end of 2015.

2.8. Pharmacovigilance

Pharmacovigilance system

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

3. Benefit-Risk Balance

Discussion on the benefit-risk balance

The 30 mg tablet strength of Iclusig has been proposed to improve patient convenience, by reducing the number of tablets per dose, when dose modifications (to 30 mg) are considered for the management of haematological and non-haematological toxicities. In addition, dose reduction may also be considered in patients with chronic phase (CP) CML who have achieved Major Cytogenetic Response.

The bioequivalence study submitted (study AP24534-14-112) has demonstrated bioequivalence between using 2 tablets of 15 mg and a single tablet of 30 mg, in order to administer a dose of 30 mg of Iclusig.

The benefit risk balance for the proposed 30 mg tablet is considered positive and in line with the benefit risk balance concluded for the 15 mg and 45 mg strengths of Iclusig in the current indications.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Iclusig is not similar to mercaptopurine, nelarabine, clofarabine, dasatinib, nilotinib, imatinib and bosutinib within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Iclusig in the treatment of 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, and Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) who are

resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the T315I mutation, is favourable and therefore recommends the granting of a new strength: 30 mg film coated tablets subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

At the request of the European Medicines Agency;

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

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

An updated RMP shall be submitted by 24 November 2014.

- **Additional risk minimisation measures**

In each Member State, the Marketing Authorisation Holder shall agree the format and content of the educational programme, including communication media, distribution modalities, and any other aspects of the programme with the National Competent Authority.

The educational programme is aimed at providing information that helps identify patients eligible for therapy, understand how ponatinib should be used safely, the risks for patients and the important adverse reactions for which monitoring and dose adjustment are recommended.

The Marketing Authorisation Holder shall ensure that in each Member State where ICLUSIG is marketed all physicians who are expected to prescribe ICLUSIG are provided with the Healthcare Professional Brochure.

Key elements of the Healthcare Professional Brochure:

• Importance of assessing the risks before starting treatment with ponatinib.

• Available data on the relationship between dose and risk of vascular occlusive events. Factors to take into account if considering dose reduction in CP-CML patients who have achieved a MCyR in the absence of an adverse event. Recommendation for close monitoring of response if a dose reduction is undertaken.

• Recommendation to consider discontinuing ponatinib if a complete haematologic response has not occurred by 3 months (90 days).

• Information on important adverse reactions for which monitoring and/or dose adjustment are recommended as outlined in the SmPC: pancreatitis, increased amylase and lipase levels, myelosuppression, liver function test abnormalities, haemorrhage, cardiac failure/left ventricular dysfunction, vascular occlusive events and hypertension.

• Instructions on management of adverse events based on monitoring and dose modifications or treatment withdrawal.

- **Obligation to complete post-authorisation measures**

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

Description	Due date
In order to determine the optimal starting dose of Iclusig and characterise the safety and efficacy of Iclusig following dose reductions after achieving MCyR in patients with CP-CML, the MAH should conduct and submit the results of a dose-ranging study.	June 2019