27 January 2022
EMA/116969/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dasatinib Accord

International non-proprietary name: dasatinib

Procedure No. EMEA/H/C/005446/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Quality

API	Active pharmaceutical ingredient
BCS	Biopharmaceutics classification system
DS	Drug substance
DSM	Drug product manufacturer
DP	Drug product
DPM	Drug product manufacturer
DoE	Design of experiments
EP/ Ph. Eur.	European pharmacopoeia
FPS	Finished product specifications
GMP	Good manufacturing practice
HDPE	High density polyethylene
IPA	Isopropyl alcohol
IPC	In-process control
LDPE	Low density polyethylene
LOD	Loss on drying
LOD	Limit of detection
LOQ	Limit of quantitation
NLT	Not less than
NMT	Not more than
PDE	Permitted daily exposure
PP	Polypropylene
PSD	Particle size distribution
QbD	Quality by design
QTPP	Quality target product profile
RPM	Revolutions per minute
RSD	Relative standard deviation
USP/NF	United States pharmacopoeia / National formula
XRD	X Ray diffraction

Clinical

AE	Adverse event
ALL	Acute lymphoblastic leukaemia
ANOVA	Analysis of variance
AUC	Area under the plasma concentration-time curve
BA	Bioavailability
BE	Bioequivalence

cCCyR	Confirmed complete cytogenetic response
CHMP	Committee for medicinal products for human use
CHR	Complete haematologic response
CI	Confidence interval
C_{max}	Maximum plasma concentrations observed after dosing
CML	Chronic myelogenous leukaemia
CMR	Complete molecular response
CNS	Central nervous system
CP	Chronic phase
CPM	Canadian product monograph
CTC	Common toxicity criteria
CV	Coefficient of variation
DMR	Deep molecular response
ECG	Electrocardiogram
EMA	European Medicines Agency
EPAR	European public assessment report
EU	European union
GCP	Good clinical practice
GLP	Good laboratory practice
GMR	Geometric mean ratio
h / hr	hour
HPLC	High pressure liquid chromatography
HZ	Hazard ratio
kg	Kilogram
l / L	Liter
LC/MS/MS	Liquid chromatography/mass spectrometry/mass spectrometry
LLOQ	Lower limit of quantitation
ln	natural logarithmic
LOQ	Limit of quantitation
LSM	Least squares mean
MAA	Marketing authorization application
MAH	Marketing authorization holder
MaHR	Major haematologic response
MCyR	Major cytogenetic response
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mL	Millilitre
MMR	Major molecular response
NEL	No evidence of leukaemia

ng	Nanogram
OS	Overall survival
P	p-value
PD	Pharmacodynamics
PFS	Progression-free survival
PH+	Philadelphia chromosome positive
PK	Pharmacokinetic
PO	Oral
QOL	Quality of life
QTc	QT interval
SmPC	Summary of product characteristics
TFR	Treatment-free remission
TKI	Tyrosine kinease inhibitor
T_{max}	Time to reach observed maximum (peak) plasma concentration
T/R	Test/reference
ULN	Upper limit of normal
ULOQ	Upper limit of quantitation

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 3 June 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Dasatinib Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 February 2019.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Dasatinib Accord is indicated for the treatment of adult patients with:

- Ph+ acute lymphoblastic leukaemia (ALL) with resistance or intolerance to prior therapy.

Dasatinib Accord is indicated for the treatment of paediatric patients with:

- newly diagnosed Ph+ ALL in combination with chemotherapy.

1.2. Legal basis, dossier content and multiples

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Sprycel instead of non-clinical and clinical unless justified otherwise

This application is submitted as a multiple of Dasatinib Accordpharma simultaneously being under initial assessment in accordance with Article 82.1 of Regulation (EC) No 726/2004. The submission of this application is due to patent grounds.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Sprycel, 20, 50, 70, 80, 100, 140 mg, film-coated tablet
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 20 November 2006
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/06/363/001-015

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Sprycel, 20, 50, 70, 80, 100, 140 mg, film-coated tabled
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 20 November 2006
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/06/363/001-015

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Sprycel, 140 mg, film-coated tabled
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 20 November 2006
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/06/363/014-015
- Bioavailability study number(s): 2185

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: John Joseph Borg

The application was received by the EMA on	3 June 2019
The procedure started on	20 June 2019
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 September 2019

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	24 September 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 October 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 April 2020
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	2 June 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 June 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 June 2020
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	11 December 2020
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 February 2021
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the applicant on	25 February 2021
The applicant submitted the responses to the 2nd CHMP consolidated List of Outstanding Issues on	22 December 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CHMP and PRAC members on	21 January 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Dasatinib Accord on	27 January 2022
The CHMP adopted a report on similarity of Dasatinib Accord with Blincyto, Iclusig, Besponsa, Xaluprine and Kymriah on	27 January 2022

2. Scientific discussion

2.1. Introduction

This centralised application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Dasatinib Accord 20/50/70/80/100/140mg film-coated tablets. The applicant is Accord Healthcare S.L.U.

The originator product is Sprycel 20/50/70/80/100/140mg film-coated tablets marketed by Bristol-Myers Squibb Pharma EEIG Ireland and first authorised in the community on 20 November 2006. (EU/1/06/363/001-015). The active substance is dasatinib as monohydrate in both products.

The applicant has applied for part of the indications of the reference product due to usage patent issues.

One bioequivalence study was conducted in support of this application using the reference Sprycel 140mg film-coated tablet marketed by Bristol-Myers Squibb Pharma EEIG Ireland and first authorised in the community on 20 November 2006 and sourced from Germany (EU/1/06/363/014-015).

Proposed indications:

Dasatinib Accord is indicated for the treatment of adult patients with:

- Ph+ acute lymphoblastic leukaemia (ALL) with resistance or intolerance to prior therapy.

Dasatinib Accord is indicated for the treatment of paediatric patients with:

- newly diagnosed Ph+ ALL in combination with chemotherapy.

It is noted that part of the indications of the reference product is covered by a usage patent.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 20, 50, 70, 80, 100, and 140 mg of dasitinib as active substance.

Other ingredients are:

Tablet core: lactose monohydrate, hydroxypropyl cellulose, cellulose, microcrystalline, methacrylic acid - methacrylate copolymer (1:2), talc, croscarmellose sodium, and magnesium stearate.

Film-coating: hypromellose (E464), titanium dioxide (E171), and medium chain triglycerides.

The product is available in Alu/Alu blisters (blisters or perforated unit dose blisters) as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of dasitinib is N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazole carboxamide corresponding to the molecular formula $C_{22}H_{26}ClN_7O_2S$. It has a relative molecular weight of 488.02 g/mol and the following structure:

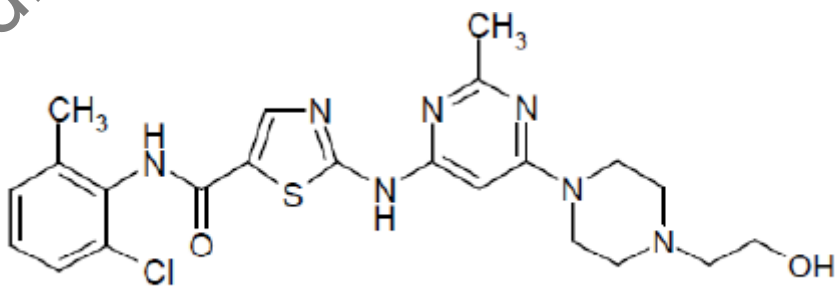

Figure: Active substance structure

The chemical structure of the active substance was elucidated by a combination of NMR spectrum, mass spectrum, infrared spectrum, UV spectrum and elemental analysis.

The active substance is a slightly hygroscopic white to off-white fine crystalline powder which exhibits pH dependent aqueous solubility. According to FDA BCS guideline, dasitinib is considered a low solubility active substance.

Optical isomerism is not possible because there is no chiral carbon in the active substance molecule.

Dasatinib is known to exist in few anhydrous and numerous solvated crystalline forms and in an amorphous form, based on literature survey and extensive polymorphism screening studies. Desired anhydrous dasatinib form is consistently obtained by the proposed manufacturing process of the active substance. All the other known anhydrous forms and solvates are not likely to be formed in the last crystallisation step and in the solvent system used or by storage of the active substance, hence, they cannot be present as impurities in the produced desired polymorphic form.

Manufacture, characterisation and process controls

An Active Substance Master File (ASMF) procedure was used to provide information on the active substance. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Dasitinib is synthesised in 2 main stages using commercially available well-defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediates, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in double PE bags with antistatic additive as primary packing, placed in multilayer PET/Al/PET/LDPE bag and introduced into cardboard drum. which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for description (visual), identification (IR, HPLC, XRD), assay (HPLC), water (Ph. Eur.), sulphated ash (Ph. Eur.), related substances (GC, HPLC), residual solvents (GC, HPLC), and particle size (laser diffraction).

The specification for dasatinib has been established based on the guidelines of ICH Q3A, ICH Q3C, ICH Q3D and ICH Q6A. Dasatinib is not listed in any of the official Pharmacopoeias.

The limits on related substances are based on analyses of so far manufactured batches of the active substance and the ICH guideline Q3A and are considered satisfactory.

According to the ICH Guideline Q3C residual solvents are class 2 and class 3 solvents in compliance with the ICH Guideline Q3C. Limits for these solvents are in line with the guideline and also tightened according to actual results.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data (3 commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 4 pilot-scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (5 ±3ºC) and for up to 6 months under accelerated conditions (25 ±2ºC / 60 ±5% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, identification, crystal form, water, assay, and related substances. The analytical methods used were the same as for release and were stability indicating.

The results so far of long term and accelerated stability studies fully meet the stability specification and no changes have been observed in the quality of the active substance. The results fully support a retest period.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months without storage conditions in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented in film-coated tablets containing 20, 50, 70, 80, 100, and 140 mg of dasitinib. The tablets are presented below:

20 mg: White to off-white, round, 5.6 mm of diameter, coated tablets debossed on one side with "DAS" and "20" on the other side.

50 mg: White to off-white, oval, 5.7 x 10.6 mm, coated tablets debossed on one side with "DAS" and "50" on the other side.

70 mg: White to off-white, round, 8.7 mm of diameter, coated tablets debossed on one side with "DAS" and "70" on the other side.

80 mg: White to off-white, triangle-shaped, 9.9 x 10.2 mm, coated tablets debossed on one side with "DAS" and "80" on the other side.

100 mg: White to off-white, oval, 7.1 x 14.5 mm, coated tablets debossed on one side with "DAS" and "100" on the other side.

140 mg: White to off-white, round, 11 mm of diameter, coated tablets debossed on one side with "DAS" and "140" on the other side.

The aim of the finished product development was to develop a generic dosage form of the reference medicinal product Sprycel tablet 20 mg, 50 mg, 70 mg, 80 mg, 100 mg and 140 mg.

Initially, the quality target product profile (QTPP) was defined based on the properties of the active substance, characterisation of the reference medicinal product, and consideration of the reference product label. Identification of critical quality attributes (CQAs) was based on the impact to patient

safety and efficacy resulting from failure to meet that quality attributes of the finished product. Pharmaceutical development focused on those CQAs that could be impacted by a realistic change to the finished product formulation or manufacturing process. For the generic medicinal product, these CQAs included assay, uniformity of dosage units, residual solvent content, dissolution, and degradation. A quality by design (QbD) approach was used to define the formulation and manufacturing process and to provide acceptable quality attributes of the generic.However, no design spaces were claimed for the manufacturing process of the finished product.

Reported literature indicates that dasatinib is a poorly soluble, highly permeable Biopharmaceutics Classification System (BCS) Class II compound. The reference medicinal product contains dasatinib monohydrate, whereas dasatinib anhydrous has been used for the development of the generic medicinal product. The data demonstrated that both forms of dasatinib (anhydrous and monohydrate) have highest solubility at pH conditions of 4.0 and below. However, in media at pH 3.0-4.0, the anhydrous form was shown to be several times more soluble than the monohydrate form.

These solubility differences lead to different *in vitro* release profiles from that of the reference medicinal product. The formulation has been developed to meet the bio-equivalence criteria. Dasatinib desired polymorphic form samples were exposed to different stress conditions and X-ray powder diffraction was performed. Preliminary stress testing was carried out on dasatinib anhydrous to study its chemical stability, impurity profile and degradation pathway and to facilitate the development of a stability-indicating method. Stressed samples were compared to the unstressed sample. The data showed that dasatinib anhydrous is labile to UV exposure and oxidative stress treatments, but stable under acidic, alkaline, and thermal (both in absence and in presence of high humidity) stresses. XRD data of studies on polymorphic stability under stressed conditions showed that dasatinib desired polymorphic form is stable under thermal, humidity, pressure and grinding stress conditions. The dasatinib desired polymorphic form is also retained after preparing the slurry with water but is converted to IPA (isopropyl alcohol) solvate after preparing the slurry with IPA.

The excipients used in the proposed generic product were selected based on those used in the reference medicinal product, the formulation development strategy and excipient compatibility studies. Most excipients and the quantities used are common in the manufacture of this type of dosage form and are considered safe in the proposed concentrations. Binary mixtures of excipients and active substance at different ratios were stored under accelerated conditions in HDPE bottles for three months and analysed. All results were within specifications; it was therefore concluded that the proposed excipients are compatible with the active sustance. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards exept the coating solution which complies with In house specifications. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

During initial stages of development, a formulation using similar excipients and manufacturing process as those of the reference product was evaluated. However, developed formulation showed that the drug release was comparable as that of the reference product. The *in vitro* dissolution method developed and validated is the QC method that is able to discriminate between good batches and reject the bad ones. The *in vivo* comparative bioavailability study conducted between the reference medicinal product Sprycel 140 mg and the proposed generic medicinal product has been shown to be comparable (C_{max} and AUC data). The T_{max} of the generic medicinal product is also relatively short at 0.75h.

A major objection (MO) was raised because of a discrepancy in dissolution profiles observed at pH 3 with two different batches. The applicant has clarified that the discrepancy in the dissolution profiles at pH 3 resulted from a batch which had a different composition, particularly with respect to binders (with

higher amounts of Eudragit), to batches which have the composition proposed for marketing. The MO was considered resolved.

The commercial manufacturing process of the finished product consists in premixing, granulation, drying, milling, blending, lubrication, compression, and coating. Several batches from different blends of the submission and validation batches were analysed and the percentage of each form of active substance in the finished product was determined based on the XRD patterns of the pure active substance. The results of these batches were compared with that of the bio batch. Polymorphic form proportions (tested by XRD) were included in both release and shelf life specifications.

As major objection (MO) on dissolution limit and discriminatory power was raised, the applicant proposed dissolution specifications (NLT 75% in 45 mins), it could be observed that the dissolution of the batch made with active substance with particles larger than the limits for PSD, would fail the dissolution test. The batch made with finer active substance, despite the increased surface area does not result in significantly faster dissolution. In both cases (made with finer and larger particles), the dissolution profiles fail similarity comparison with the bio batch. Thus, with limits in place for the active substance PSD and dissolution, the finished product performance can be ensured. The MO was considered to be resolved.

Comparative bioavailability studies under fasting conditions was performed to assess the bioequivalence of formulation of pivotal batch after a single oral dose administration. In the pivotal bioequivalence study, the comparison was made between the proposed generic medicinal product and the EU reference medicinal product. The results presented showed that the criteria used to assess bioequivalence between the generic and reference formulations were fulfilled. The Test to Reference ratio of geometric LS means and corresponding 90% confidence interval for Cmax, AUC0-T and AUC0-∞ were all within the acceptance range of 80.00 to 125.00%.

A biowaiver for 20, 50, 70, 80, and 100 mg strengths was applied by the applicant. In support to this request, the applicant stated that all strengths are dose proportional; however this was not considered to be sufficient justification on its own. In order to demonstrate similarity between the bio batch and all the remaining strengths, comparison of dissolution profiles of the highest strength of the bio batch to the dissolution profiles of all the remaining strengths (without surfactant) at pHs 1.2, 4.5 and 6.8 was provided and considered satisfactory.

No data was provided on the proportions of polymorphic forms in the batches used for the request of biowaiver, therefore, it could not be confirmed that all batches of all strengths to be manufactured routinely will have the same proportions of polymorphic forms as the biobatch. This precluded the granting of the biowaiver. Therefore, the CHMP concluded that the biowaiver may only be granted if a limit for both anhydrous and solvate polymorphic form proportions is included in the release and shelf life specification of all strengths. The applicant agreed to include a limit for both anhydrous and solvate polymorphic form proportions in the release and shelf life specification of all strengths and the issue was considered solved.

A risk assessment of the overall finished product manufacturing process was performed to identify the high-risk steps that may affect the CQAs of the finished product. Subsequently, the CQAs of intermediates from each process step that impact the finished product CQAs were identified.

For each process step, a risk assessment was conducted to identify potentially high-risk process variables which could impact the identified intermediate CQAs and, ultimately, the finished product CQAs. These variables were then investigated to better understand the manufacturing process and to develop a control strategy to reduce the risk of a failed batch.

Several trials were made with active substance having different particle size distribution (PSD) values to evaluate the effects of particle size on assay and content uniformity of the finished product. Based

on the results, there was no significant difference observed among the batch manufactured with different PSDs of active substance. All results met the specifications. The PSD specification was determined based on the range evaluated during process validation.

Effects of the binders, disintegrant, lubricant, and coating level were studied. As a result of these studies, the commercial formulation of the finished product was selected.

The primary packaging is Alu/Alu blisters (blisters or perforated unit dose blisters). 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

The manufacturing process consists of 10 main steps: weighing, sieving, mixing, wet granulation, drying, blending, lubrication, compression, film-coating and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies in tablets blend and tablets 20, 50, 70, 80, 100 and 140 mg. The validation was performed on six commercial scale batches of dasatinib tablets blend. The two extremes of tablet strength (20 & 140 mg) were validated with 3 commercial scale batches each. The 100 mg strength was also validated with 3 batches. The validation was performed on one batch for the intermediate strengths: 50, 70 and 80 mg. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner, however the CHMP recommended to carry out the leak test for packaging integrity and visual checks during commercial phase full scale packaging validation and submit the data via a variation. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form description (visual), identification (HPLC, UV), assay (HPLC), uniformity of dosage unit (HPLC), dissolution (UPLC), degradation products (HPLC), residual solvents (GC-HS), water (Ph. Eur.), disintegration (Ph. Eur.), polymorphic forms (XRD), and microbial limit tests (Ph. Eur). The specifications are the same for all strengths, except the description which include "20", "50", "70", "80", "100", and "140" mg depending on the strength.

In the context of reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action (Decision tree for the principles for setting specifications based on the dissolution results of the bio batch), immediate release is identified as at least 75% (Q) of the active substance is dissolved within 45 minutes. The Q derives from the Ph. Eur. (5.17.1) recommendation for conventional release dosage forms. Therefore, in line with the reflection paper, the applicant was asked as major objection to set a single dissolution specification of NLT 75% in 45 minutes or else set a specification for more than one time point. The finished product specifications limit was amended as requested.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 batches using a validated ICP-OES method was provided, demonstrating that each relevant elemental impurity does not exceed their PDE, nor their control thresholds. Based on the risk assessment, it can be concluded that it is not necessary to include any elemental impurity controls.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been requested as major objection considering all suspected and actual root causes in line with the

"Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis results are provided for 12 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 12 commercial scale batches of finished product stored for up to 24 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, dissolution, degradation products, water, disintegration, polymorphic forms and microbial limit. The analytical procedures used are stability indicating.

A reduced design has been considered in line with the ICH Q1D guideline. As defined on ICH guidelines, topic Q1D: "bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size and/or fill) are tested at all time points as in a full design". A reduced design of stability study, more precisely, bracketing was chosen, seen that the formulation of all the strengths is identical and materials of the container closure system are the same for all the strengths. The selected approach, regarding the exhibit batches, is to follow in stability three batches of each extreme strength and one batch of each intermediate strength.

The long-term stability studies conducted on the finished product demonstrate that the all parameters meet the specifications with the exception of dissolution, for a period of 24 months for all batches under stability. Results also conform after 6 months under accelerated stability conditions in the proposed container closure system for all batches that are part of the stability program.

Before a shelf life (and associated storage conditions) and a hold time was granted, the applicant was asked, as major objection, to address all the observations related to the intra- and inter-batch variability in dissolution results of stability batches and provide more long-term stability data. The applicant did not provide data of the original stability batches at 36 months but restarted stability studies afresh. The applicant was reminded that new time points should be tested at a specification of NLT 75% (Q) at 45 minutes and stability studies should include tests for proportions of the polymorphic forms in the finished product. In line with the CHMP comments, the dissolution limit in the shelf life specifications was tightened by the applicant to NLT 75% (Q) in 45 minutes and additional data was generated on new batches. Twelve validation batches were, stored in bulk, packaged in blisters and then followed in long-term and accelerated conditions. All dissolution results performed on the validation batches meet the revised dissolution limit NLT 75% (Q) at 45 minutes for a period of 6 months. All these batches were stored in bulk for 9 months before being packaged in blisters. All the

stability results from the new batches met the new established dissolution limits NLT 75% (Q) at 45 minutes. Given that, for the stability studies of the validation batches, the applicant only provided dissolution values, the results of the previously submitted batches are being taken into consideration to inform on the other stability parameters and grant the shelf life. No concerns remained outstanding following the assessment of the other stability parameters during previous rounds of this procedure. Since there is currently 6 months' real time stability data available, the shelf life granted in line with ICH Q1E is 12 months. Polymorphic form proportions have not been evaluated in stability studies so far but, due to the inclusion of limits for such proportions in both the release and shelf-life specifications these are to be included in stability studies from this point onwards.

Forced degradation study was carried out on the finished product in solution and power, the effects of acid, alkaline, ultraviolet irradiation, thermal and oxidation stresses on the finished product were studied and the resulting degradation products were monitored. The forced degradation study of the finished product in solution has shown that finished product is sensitive to all stress treatments, forced degradation evaluation on powder samples has shown relatively good stability showing a slight degradation of the finished product.

In addition, five batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. It has been concluded that the finished product is not sensitive to light.

A bulk stability study was performed to propose a bulk holding time period for the bulk tablets. The bulk tablets are packed in the designated packaging material for bulk storage. The batches are stored under ICH controlled conditions 25°C ± 2°C, 60 % RH ± 5% for 9 months. The testing is performed initially, at 3 months, 6 months and 9 months. The results between the bulk tablets and the packaged batches of identical stations do not show significant differences. Another bulk stability study was conducted where the dissolution specification was NLT 75% (Q) in 45 minutes; tablets were tested initially and after 9 months and the dissolution specification was met. It is therefore possible to conclude that the product can be kept in bulk tablets for a period of 9 months before being packaged in the proposed container closure system.

Based on available stability data, the proposed shelf-life of 12 months without any special storage conditions as stated in the SmPC (section 6.3) are acceptable.

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.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. 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.

A number of issues were raised by CHMP as Major Objections (MO). The MOs were related to formulation, dissolution of the finished product, presence of polymorphic forms of the active substance

in the finished product, the strength biowaivers, primary packaging material, dissolution specifications of the finished product, risk evaluation of nitrosamines and stability of the finished product. The issues were resolved satisfactorily by the applicant as described above.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertains to carry out the leak test and visual checks during commercial phase full scale packaging validation and submit the data via a variation. This point is put forward and agreed as recommendations for future quality development.

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 viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- to carry out the leak test and visual checks during commercial phase full scale packaging validation and submit the data via a variation.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Dasatinib Accord manufactured by Accord Healthcare S.L.U. is considered unlikely to result in any significant increase in the combined sales volumes for all dasatinib containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

The applicant has used isopropyl alcohol to "enhance" the solubility of the dasatinib (presenting better dissolution profile). This was to be removed during the manufacturing process. However the applicant was asked to discuss the possible formation of a solvate with isopropanol and the possible impact in terms of safety. The applicant responded that the proposed release specification for isopropanol ensures that the total daily exposure to isopropanol from Dasatinib Accord tablets will be below the established PDE of 50 mg/day (Impurities: Guideline for residual solvents Q3C (R6). ICH. 20 October

2016), thereby representing a safe exposure level when used according to the recommended posology of the drug product. The applicant's position is considered justified and thus acceptable.

2.3.4. Conclusion on the non-clinical aspects

There are no objections to approval of Dasatinib Accord from a non-clinical point of view. The non-clinical parts of the SmPC of the generic product are identical to those of the reference product.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing dasatinib. To support the marketing authorisation application the applicant conducted 1 bioequivalence study with cross-over design under fasting conditions. This study was the pivotal study for this application.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of dasatinib based on published literature. The SmPC is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) in their current version and Dasatinib product-specific bioequivalence guidance (EMA/CHMP/675838/2014) version 1 in its current version (Rev1/2020), are of particular relevance.

GCP aspect

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

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

Exemption

The applicant has submitted one fasting bioequivalence (BE) study in support of this application, and this was performed using the highest strength (140mg film coated) claiming an exemption for the lower strengths. To support the strength biowaiver the applicant stated that all strengths have the same manufacturer and qualitative composition, are dose proportional and present comparable in vitro dissolution profile as the reference product in line with the requirement of the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98/Rev.1/ Corr). This is further discussed in the quality part of this report.

The conduct of a single BE study with the highest strength under fasting conditions was in line with the dasatinib product-specific bioequivalence guidance (EMA/CHMP/675838/2014) version 1 in effect when the application was submitted. However during the procedure the guidance was updated (EMA/CHMP/675838/2014/Rev1/2020) and a fed study was also requested. During the assessment the applicant submitted results of a fed study performed with the 100mg strength using the US reference to respond to issues raised. The fed study was not required during the submission and therefore is only considered as supportive.

Tabular overview of clinical studies

To support the application, the applicant has submitted 1 bioequivalence study.

Type of study	Study No.	Objective(s) of the study	Study design	Test Product(s); Dosage; Route of administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	2185	To compare the bioavailability of dasatinib from Dasatinib 140 mg tablets and Sprycel® 140 mg film-coated tablets in healthy, non-smoking male volunteers under fasting conditions.	Single-Dose, Randomized, Open-Label, Four-Way Fully Replicate, Fasting State	Dasatinib 140 mg tablets; Single dose of 140 mg; Oral	60	Healthy Male subjects	Single dose	Complete; Full

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study 2185: A Single-Dose, Randomized, Open-Label, Four-Way Fully Replicate, Pivotal, Bioequivalence Study of Dasatinib 140 mg Film-coated Tablets (Pharmascience Inc., Canada) and SPRYCEL (dasatinib) 140 mg Filmcoated Tablets (Bristol-Myers Squibb Pharma EEIG, UK) in Healthy Male Volunteers under Fasting Conditions

- **Study design**

The applicant has submitted a comparative bioequivalence study protocol number 2185 version number 01 dated 20 October 2017 which was approved by the Optimum Ethics Review Board, Ontario, Canada on 25 October 2017.

This was a randomised, balanced, open label, single dose, four-way fully replicate, two sequence, two treatment, comparative oral bioavailability study to establish comparative bioequivalence of dasatinib 140 mg film-coated tablets (Pharmascienice Inc, Canada) and Sprycel (dasatinib) 140 mg film-coated tablets (MAH: Bristol-Myers Squibb Pharma EEIG, UK) in 60 healthy, adult male subjects under fasting conditions. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety and tolerability of a single dose of dasatinib 140 mg.

The study centre was BioPharma Services Inc Canada. The studies were conducted between 29 November 2017 and 13 February 2018 and bioanalysis was performed between 02 January 2018 and 11 January 2018.

Subjects who met the eligibility criteria were randomly assigned to receive the study drugs according to one of the two dosing sequences A-B-A-B or B-A-B-A. A total of 30 subjects were planned to receive treatment sequence A-B-A-B and 30 subjects were planned to receive sequence B-A-B-A.

Subjects randomised to the A-B-A-B sequence received the test product (Treatment A: Dasatinib 140 mg tablets) in period 1 and period 3, and then following a 7 days washout period, received the reference product (Treatment B: Sprycel 140 mg film-coated tablets) in period 2 and period 4.

Subjects randomised to the B-A-B-A sequence received the reference product (Treatment B) in period 1 and period 3, and then following a minimum 7 days washout period, received the test product (Treatment A) in period 2 and period 4. The washout period of at least 7 days was estimated to be adequate in avoiding carry-over effects of the preceding treatments.

Subjects were dosed consecutively according to the randomisation scheme beginning at 08:01 on:

November 30, 2017 for Period 1, December 07, 2017 for Period 2, December 14, 2017 for Period 3, and December 21, 2017 for Period 4.

Based on the randomised schedule and following an overnight fast of at least 10 hours in both periods each volunteer received their assigned formulation with 240 ± 3 mL of ambient temperature water at their scheduled timepoint. Subjects were instructed not to touch, chew, bite or break the study drug. No fluid was allowed from one hour before dosing until one hour after dosing. Subjects were dosed while in sitting posture and were instructed to remain seated in an upright position for the first 4 hours following drug administration.

Blood samples were taken at the following time points: pre-dose and at 0.17, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after dosing. Blood sampling time adjustments are presented in the dossier.

- **Test and reference products**

Table 1: Test and reference product information

Product charachteristics	Test product	Reference product
Name	Dasatinib	Sprycel
Strength	140 mg	140 mg
Dosage form	Film-coated tablets	Film-coated tablets
Batch number	P-2631	AAH3634
Batch Size (biobatch)	Complied with the requirement of the BE guidelines	
Measured content (% labelled claim)	97.2%	96.6%
Expiry date (retest date)	Retest date: 12-2017	Expiry date: 03-2018
Member state where the reference prduct was purchased		Germany
The product was used in the following trials	2185	2185

- **Population(s) studied**

60 healthy adult male human subjects were enrolled as per the protocol. The study started with 60 subjects and 56 completed the study.

Main inclusion criteria:

Subjects met the following inclusion criteria within 30 days prior to Period 1 dosing:

1. Healthy, non-smoking (for at least 6 months prior to first study drug administration), male volunteers, 18 years of age and older.

2. BMI between 18.5 and 30.0 kg/m², inclusive.

3. Healthy, according to the medical history, ECG, vital signs, laboratory results and physical examination as determined by the PI/Sub-Investigator.

4. QTc interval < 430 milliseconds, unless deemed otherwise by the PI/Sub-Investigator.

5. PR interval between 120 and 200 milliseconds, inclusive and QRS interval <120 milliseconds, unless deemed otherwise by the PI/Sub-Investigator.

6. Systolic blood pressure between 95-140 mmHg, inclusive, and diastolic blood pressure between 55-90 mmHg, inclusive, and heart rate between 50-100 bpm, inclusive, unless deemed otherwise by the PI/Sub-Investigator.

7. Clinical laboratory values within BPSI's most recent acceptable laboratory test range, unless values are deemed by the PI/Sub-Investigator as "Not Clinically Significant".

8. Ability to comprehend and be informed of the nature of the study, as assessed by BPSI staff. Capable of giving written informed consent prior to receiving any study medication. Able to communicate effectively with clinic staff.

9. Ability to fast for at least 14 hours and consume standard meals.

10. Availability to volunteer for the entire study duration and willing to adhere to all protocol requirements.

11. Agreed not to have a tattoo or body piercing until the end of the study.

12. Agreed not to drive or operate heavy machinery if feeling dizzy or drowsy following study drug administration until full mental alertness was regained.

13. Agreed not to donate sperm during the study and until 90 days after the last study drug administration.

14. Men who were able to impregnate a female agreed to use medically acceptable methods of contraception during the study and for 90 days after the end of the study.

Medically acceptable methods of contraception include using a condom with spermicide with a female partner of child-bearing potential who was using oral contraceptives, hormonal patch, implant or injection, intrauterine device, or diaphragm with spermicide. Complete abstinence alone could be used as a method of contraception.

Participant unable to procreate; defined as surgically sterile (i.e., has undergone a bi-lateral vasectomy at least 6 months prior to the first administration of the study drug).

If a subject's partner became pregnant during his participation in the study and for 90 days after he had completed his last study drug administration, he must have informed BPSI staff immediately.

Protocol deviations:

Period 1: 27 samples (15 for the test and 12 for the reference) were aliquoted with 1 minute delay after centrifugation.

Period 2: 3 subjects checked in late resulting in less than advised confinement time.

Period 4: 1 subject checked in late resulting in less than advised confinement time

2 samples (1 for the test and 1 for the reference) were centrifuged with 2 minutes delay after collection).

Drop outs:

Two subjects withdrew voluntarily from the study and two subjects were removed by the Investigator due to testing positive for drugs of abuse.

- **Analytical methods**

Analysis of dasatinib was performed using test method RDPM257. This Ultra Performance Liquid Chromatography Method with Tandem mass spectrometry method involved the extraction of Dasatinib d8 (internal standard) from human plasma. Throughout sample collection and following centrifugation, the samples were maintained in an ice-bath until stored in the freezer. All plasma samples were shipped by courier in dry ice, and the first set of samples were received frozen and in good condition by the bioanalytical facility on 28 December 2017.

Total long-term plasma stability has been provided for 100 days at nominal temperature of -20°C and 28 days at nominal temperature of -70°C which covers the 42 days at -20°C (November 30, 2017 – January 11, 2018) from the first collection date to last extraction date.

4618 blood samples were expected and 4618 were received. All the samples received were analysed.

Bioanalytical report: The bioanalytical report dated 2 March 2018 was submitted with 20% of the subject chromatograms presented as well as the method SOP. Dasatinib d8 was used as an internal standard (IS) and was sourced from TLC Pharmaceutical Standards. Certificates of analysis for the test and reference drug products as well as for the drug standards used for dasatinib and the internal standard dasatinib d8 have been provided and are deemed acceptable.

The inter day coefficient of variation (%CV) for the quality control samples at concentrations of 3.00 ng/mL (QC A), 100.00 ng/mL (QC B), 160.00 ng/mL (QC C) and 40.00 ng/mL (QC D) were 3.6%, 2.4%, 2.8% and 2.7% respectively and the inter day % Bias were 0.2%, 0.0%, 1.0% and 0.7%, respectively.

Calibration range: 1.00ng/ml to 200.00 ng/ml (8 point curve)

Reanalysis: 101 samples were re-assayed (2.2%). There were 86 re-assays for COACR (concentration outside accepted calibrated range) and 15 re-assays for LS (lost sample). The reason for their repeats was documented and presented.

Incurred Sample Reanalysis: 288 samples were identified for incurred sample reanalysis however they did pass the set limits: The total of 100.00% ISR samples were found to be within ±20% of the mean of their original assay values.

Validation of the test method: The method was validated (RDPV257) in February 2017. The following parameters were addressed; selectivity and specificity of dasatinib and the internal standard (IS), calibration curve (linearity), carryover test, matrix effect precision and accuracy, LLOQ and ULOQ, recovery of both the analyte and the internal standard, intra and inter assay precision and accuracy, dilution integrity accuracy and precision, freeze-thaw (4 cycles), long term stability at -20°C and -70°C, lipaemic effect precision and accuracy, haemolysis effect accuracy and precision, concomitant medication interference (acetaminophen, caffeine, chlorpheniramine, ibuprofen, naproxen, pseudoephedrine) and metabolite interference (metabolites 4'-hydroxy dasatinib and dasatinib N-oxide), short term stability (bench top) at room temperature, processed sample stability at 4°C, stock solution stability of dasatinib and internal standard at -20°C and at room temperature, Internal standard working solution stability at 4°C and at room temperature. Each parameter has been assessed and the limits are justified. This is deemed acceptable.

Pharmacokinetic variables

Primary parameters: AUC_{0-t}, AUC_{0-inf} and C_{max}

Secondary parameters: T_{max}, Residual area, Elimination rate constant, $T_{1/2}$

- **Bioequivalence criteria;** Bioequivalence was concluded if the 90% confidence interval of geometric mean of Cmax, AUC0-t and AUC0-inf between test and reference products fall within the range of 80.00 % to 125.00 % for Dasatinib.
- **Statistical methods**

Descriptive statistics (min, max, median, mean, standard deviation and coefficient of variation) of all PK parameters were to be provided for dasatinib for the test and reference products.

The within-subject standard deviation (SWR and SWT) of the test and the reference products was to be determined for the ln-transformed pharmacokinetic parameters AUCt, AUCinf and Cmax.

The inter-subject and intra-subject CV were to be calculated for the in-transformed pharmacokinetic parameters AUCt, AUCinf and Cmax.

Average bioequivalence was to be used to determine bioequivalence first. If bioequivalence was not met for Cmax, scaled-average-bioequivalence could have been used if both of the following conditions are met:

- The point estimate of the geometric mean ratio was within the 80.00- 125.00% range;
- The reference-to-reference within-subject coefficient of variation (CV) was > 30%, and was not the result of outliers

Average Bioequivalence

ANOVA including sequence, subjects nested within sequence, period and treatment was to be performed on the ln-transformed data for AUCt, AUCinf and Cmax.

The 90% CI of the test/reference ratios of geometric means for AUCt, AUCinf and Cmax was to be calculated based on the LSMEANS and ESTIMATE of the ANOVA.

Results

Table 2: Pharmacokinetic parameters for dasatinib 140mg (fasting) (non-transformed values)

Pharmacokinetic parameter	Geometric Means (±CV%)	
	Test product[1]	Reference Product[2]
$AUC_{(0-t)}$ (ng.h/mL)	441.94 (±150.87)	457.40 (±225.92)
$AUC_{(0-\infty)}$ (ng.h/mL)	461.00 (±154.62)	486.67 (±220.09)
Cmax (ng/mL)	126.98 (±55.27)	154.57 (±88.91)
tmax[3] (h)	0.75 (0.25 - 5.00)	1.00 (0.50 – 5.05)

[1] pms-Dasatinib 140 mg tablets (Pharmascience Inc., Canada)
[2] Sprycel® (dasatinib 140 mg tablets) (Bristol-Myers Squibb Pharma EEIG, UK)
[3] Median (Min, Max)

Table 3: Statistical analysis for dasatinib 140mg (fasting) (in-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio (%)	Confidence Intervals (%)	CV%[1]
Test product / Reference product			
AUC_t	109.08	99.43 - 119.66	43.04
AUC_{inf}	102.57	95.11 - 110.61	33.85
C_{max}	94.05	83.98 - 105.34	53.85

[1]Estimated from the Residual Mean Squares. For replicate design studies report the within-subject CV% using only the reference product data.

Outliers

Upon review of the concentration data, it was noted that **subject 34** demonstrated concentration values that were below the limit of quantitation (BLQ) for periods 1, 3, and 4, while having demonstrated measurable concentration values for period 2 only. Since subject 34 does not fulfil the PK data set criteria defined in section 11.1 of the protocol, which states that subjects should have measurable concentration data from at least two periods, data from subject 34 was not included in the PK stats analysis and is instead presented separately.

Initially, data from all 56 subjects who completed, and demonstrated measurable concentration values for, at least 2 periods of the study were included in the PK stats analysis, as per protocol.

It was noted that **subject 60** demonstrated very low concentration values for both reference arms, where their individual AUC values for the reference were less than 5% of the geometric mean AUC value of the reference product, which was calculated upon exclusion of their data. As per protocol, the data obtained from the reference arms for subject 60 were to be excluded from PK stats analysis. However, since both sets of reference data were excluded, the entirety of concentration data obtained from subject 60 were omitted from PK stats analysis, since a test/reference comparison was no longer possible. Data from 55 subjects were included in the final PK stats analysis.

Subject **52 and 54** demonstrated very low concentration values in period 2, after both having been dosed with the reference. Both subjects showed individual AUC values for the reference during period 2 that were less than 5% of the geometric mean AUC value of the reference product, which was calculated upon exclusion of their data. Period 2 data was excluded from PK stats analysis for subjects 52 and 54.

Table 4: Pharmacokinetic parameters for dasatinib 140mg (fasting n=56) (non-transformed values) including subject 60 and period 2 for subjects 52 and 54

PK Parameter	Trt A / Trt B Geometric Mean Ratio (%) and (90% Confidence Interval (%))	Intra-Subject CV (%)
AUC_t	123.96 (108.48 - 141.66)	66.23
AUC_{inf}	110.68 (100.40 - 122.02)	45.12
C_{max}	105.51 (91.65 - 121.47)	70.69

- **Safety data**

There were 46 adverse events involving 20 subjects in this study. No serious AEs were reported during the conduct of this study.

There were 23 AEs associated with 15 subjects who received treatment A (test). There were three instances of diarrhoea after administration with treatment A in this study.

There were 23 AEs associated with 12 subjects who received treatment B (reference). There were three instances of diarrhoea and one instance of vomiting after administration with treatment B in this study.

All subjects underwent urine tests for drugs of abuse, cotinine, and an alcohol test at check-in for each study period. All test results at check-in for drugs of abuse, cotinine, and breath alcohol were negative with the exception of test results for subjects 36 and 51 who were positive to DOA test at period 2 check-in. Both subjects were dismissed from the study due to this positive test.

In addition, a complete blood count (CBC) was performed on all subjects at each period check-in. All test results at check-in for complete blood count were within normal range or deemed Not Clinically Significant by the Investigator.

The clinical laboratory tests (haematology, serum chemistry and urinalysis) were repeated prior to discharge at the end of the study or after termination of subjects from the study. There were no screening, on study or post-study laboratory results outside of normal range that were deemed Clinically Significant by the Investigator.

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.2.3. Additional data

2.4.3. Discussion on clinical aspects

The results discussed above show that the PK parameters of the bioequivalence study pass the requirements of the guideline on the Investigation of Bioequivalence where the applicant states that the 90% confidence intervals calculated for the primary parameters C_{max} and AUC_{0-t} for dasatinib fall within the 80.00 – 125.00% acceptance range after single dose administration under fasting conditions. The submission of a single BE study in the fasted state was in line with the requirements of the product-specific BE guidance for dasatinib at the time the application was submitted.

It is noted that the product-specific BE guidance for dasatinib has since been revised. It specifically mentions the issue of outliers (these were the cause of concern in the major objection raised at day 120). In fact the guideline states that "Some subjects may randomly exhibit low concentrations of dasatinib when taking dasatinib products in the fasted state. Therefore, these products are considered with specific formulation characteristics and, consequently, bioequivalence should be evaluated under fasting and fed conditions"

Hence a major objection was raised by the CHMP and the applicant was asked to discuss the issue of variabilitiy in dasatinib exposure in that some subjects which may randomly exhibit low concentrations of dasatanib when taking dasatinib products in the fasted state. As these products are considered with specific formulation characteristics and bioequivalence should be evaluated under fasting and fed conditions the applicant was asked to address the lack of a fed study and to assess the impact of food on the variability of this product. The applicant was requested to justify providing a fasting study only taking account of the Guideline on the investigation of Bioequivalence where "subjects with very low plasma concentrations may be excluded if AUC is less than 5% of reference medicinal product geometric mean AUC."

The applicant submitted a fed study on the 100 mg strength compared to the US innovator product for dasatinib using parameters approved by FDA for variable drugs. The results of sasatinib fed study have been re-analysed against EMA bioequivalence criteria and statistical method. The test product dasatinib

100 mg film-coated tablets demonstrated a comparable extent of absorption of dasatinib to the reference product Sprycel (dasatinib) 100 mg film-coated tablets with a test/reference (T/R) geometric mean ratios (GMR) of approximately 97% for AUCt, with the corresponding 90% CI contained within the EMA-acceptance range 80.00% - 125.00%. The test product also demonstrated a comparable rate of absorption of dasatinib to the reference product with a T/R GMR of approximately 86% for Cmax within the EMA-acceptance range 80.00% - 125.00% and corresponding 90% CI contained within the EMA-widening acceptance range 78.25 - 127.80%. In parallel, the applicant performed a physicochemical comparison of the EU reference and US reference product Sprycel comparing also their dissolution profiles illustrating their similarity.

The fed study falls within the acceptance range for 90%CI for the AUC but not for the Cmax. The geometric mean ratios are 97% for AUCt and 85% for Cmax. For Cmax the 90% CI are contained within the EMA-widened acceptance range 78.25 - 127.80% for variable drugs. The applicant seems to be using the FDA reference scaled and unscaled bioequivalence system for variable drugs. The applicant concluded that in line with the protocol and based on the results of the reference scaled and unscaled approach, BE is demonstrated under fed conditions.

The study is considered to be supportive of the argument requested in the major objection but not valid for the EU since the reference product used is sourced from the US market and since it is not performed on the highest and most sensitive strength. The major objection raised due to the change of EU guidance after submission was therefore considered to be resolved.

In terms of safety a total of 22 mild and 1 moderate AEs were experienced by the subjects after taking the test product. A total of 21 mild and 2 moderate AEs were experienced by the subjects after taking the reference product. No AEs associated with clinical laboratory tests were experienced by the subjects at post-study. No serious adverse events were reported during the conduct of this study. The two products exhibited a similar safety profile.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence study 2185, dasatinib 140mg film-coated tablets is considered bioequivalent with Sprycel 140mg film-coated tablets (dasatinib) in normal, healthy, male volunteers under fasting conditions. This application was submitted prior to the publication of the updated product specific bioequivalence guideline for dasatinib hence a fasting study is appropriate. A supportive fed study was also submitted however this cannot be considered as an extra study since the reference product used is that of the US and the study was done on the 100mg strength (which is not the highest strength in the range proposed.)

The results of study 2185 with 140mg formulation can be extrapolated to other strengths 20mg, 50mg, 70mg, 80mg, and 100mg, according to conditions in the relevant Guidelines (refer to the quality sections for further information).

The product is approvable from a clinical point of view and all issues have been resolved.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns	
Important identified risks	Myelosuppression Fluid retention

Summary of safety concerns	
	Bleeding related events QT prolongation Pulmonary Arterial Hypertension (PAH) Pregnancy related malformative or foeto/ neonatal toxicity
Important potential risks	Severe hepatotoxicities Direct cardiotoxic effects (e.g., Cardiomyopathy) Growth and development disorders and bone mineral metabolism disorders in the paediatric population Toxic skin reactions CYP3A4 drug interactions HBV reactivation Nephrotic syndrome
Missing information	Carcinogenicity Paediatric data: Children < 1 year of age Reproductive and lactation data

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

None.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 is acceptable.

In addition, the following minor revisions are recommended to be taken into account with the next RMP update:

In addition, minor revisions were recommended to be taken into account with the next RMP update:

Part III: Pharmacovigilance plan

Other targeted follow-up measures: The applicant is encouraged to implement targeted follow-up measures to ensure complete data on the paediatric cases and cases of relevant serious cardiac events.

Annex 4

Pulmonary Arterial Hypertension (PAH) questionnaire: The applicant should ensure that information on patient ID, product name and batch number is obtained. The applicant should consider collecting information on additional laboratory parameters performed in relation to the PAH.

2.6. Pharmacovigilance

2.6.1. 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.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

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

3. Benefit-risk balance

This application concerns a generic version of dasatinib film-coated tablets. The reference product Sprycel is indicated for

the treatment of adult patients with:

- Ph+ acute lymphoblastic leukaemia (ALL) with resistance or intolerance to prior therapy.

and

the treatment of paediatric patients with:

- newly diagnosed Ph+ ALL in combination with chemotherapy.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a randomised, two-period, two-treatment crossover design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Dasatinib Accord met the protocol-defined criteria for bioequivalence when compared with the Sprycel. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-72h, and Cmax were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Dasatinib Accord is not similar to Blincyto, Iclusig, Besponsa, Xaluprine and Kymriah within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Dasatinib Accord is favourable in the following indication:

Dasatinib Accord is indicated for the treatment of adult patients with:

- Ph+ acute lymphoblastic leukaemia (ALL) with resistance or intolerance to prior therapy.

and

Dasatinib Accord is indicated for the treatment of paediatric patients with:

- newly diagnosed Ph+ ALL in combination with chemotherapy.

The CHMP therefore recommends the granting of the marketing authorisation 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).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

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.