30 May 2024
EMA/313181/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dasatinib Accord Healthcare

International non-proprietary name: dasatinib

Procedure No. EMEA/H/C/006251/0000

Note

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

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List of abbreviations

AAS	Atomic Absorption Spectrometry
AP	Applicant's Part (or Open Part) of a ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
AS	Active substance
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AUC	Area under the plasma concentration curve
AEs	Adverse events
ALL	Acute lymphoblastic leukaemia
AE	Adverse event
Afssaps	French Health Products Safety Agency
AGES	Austrian Agency for Health and Food Safety GmbH
ALT	Alanine aminotransferases
ANOVA	Analysis of variance
AST	Aspartate aminotransferases
AUC	Area under the curve
AUC0-24h	Area under the plasma concentration-time curve from time zero to 24 hours
AUC0-∞	Area under the plasma concentration-time curve from time zero to infinity
BCS	Biopharmaceutics Classification System
BMI	Body mass index
BCS	Biopharmaceutics Classification system
BID	Twice daily
BCR-ABL	Breakpoint cluster region-abelson
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
CHR	Complete HR
CML	Chronic myeloid leukaemia
CML-AP	Chronic myeloid leukaemia in accelerated phase
CML-CP	Chronic myeloid leukaemia chronic phase
CML-BP	Chronic myeloid leukaemia blast phase
Cmax	Maximum measured concentration of drug in plasma
Cmin	Minimum measured concentration of drug in plasma
CoA	Certificate of Analysis
^{14}C :	Radioactive Carbon
CCyR	Complete cytogenetic response
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CoA	Certificate of Analysis
CoS	Certificate of Suitability
CP	Centralised (Application) Procedure
CRS	Chemical Reference Substance (official standard)
CRT	Controlled Room Temperature
CTM	Clinical Trial Management
CQAs	Critical Quality Attributes
CDSCO	The Central Drugs Standard Control Organisation
CI	Confidence interval
CPMP	Committee for Proprietary Medicinal Products
CrCl	Creatinine clearance
CYP	Cytochrome P450
DAD	Diode Array Analysis
DOE	Design of Experiments
DPM	Drug Product Manufacturer
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicine Agency
EP	European Pharmacopoeia
EC	Commission Regulation
EWP	The Efficacy Working Party
FDA	Food and Drug Administration
FPM	Finished Product Manufacturer

GC	Gas Chromatography
GCP	Good clinical practice
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPLC	High Performance Liquid Chromatography
HR	Hematologic response
hr	Hour
HQC	High quality control
INN	International non-proprietary name
IPC	In-process control
IPF	Idiopathic pulmonary fibrosis
IR	Infrared
ICH	International Council for Harmonisation
ICMR	The Indian Council of Medical Research
IEC	Independent ethics committees
IL	Interleukin
IPF	Idiopathic pulmonary fibrosis
IR	Infrared
IS –	Internal standard
KF	Karl Fischer titration
K3EDTA	Tripotassium ethylenediaminetetraacetic acid
LC-ESI-MS/MS	Liquid Chromatography–Electrospray Ionization Tandem Mass Spectrometry
LLOQ	The lower limit of quantification
LQC	Laboratory Quality Control
LDPE	Low Density Polyethylene
LOD	Limit of Detection or Loss on Drying
LOQ	Limit of Quantitation
LoQ	List of Questions
LT	Less than
LBP-CML	Lymphoid blast phase- Chronic myeloid leukaemia
MAA	Marketing Authorization Application
MaHR	Major hematologic response
MBP-CML	Myeloid blast phase-Chronic myeloid leukaemia
MCyR	Major cytogenetic response
Mg	milligram
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MEB	Medicines Evaluation Board
MS	Mass Spectrometry
MF	Matrix factor
MHRA	Medicines and Healthcare products Regulatory Agency
MQC	Middle quality control
ND	Not detected
NF	National Formulary
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
ng	Nanogram
nmol/L	Nanomolar per ml
OS	Overall survival
OOS	Out of Specifications
OC	Other concern
OECD	The Organisation for Economic Co-operation and Development
PDE	Permitted Daily Exposure
Ph. Eur.	European Pharmacopoeia
pH	Potential of Hydrogen
PIL	Patient Information Leaflet
PVC	Poly vinyl chloride
PVDC	Polyvinylidene chloride
PXRD	Powder X-Ray Diffraction
PD	Pharmacodynamic
PFS	Progression-free survival
Ph+(ALL)	Philadelphia chromosome positive acute lymphoblastic leukaemia
PK	Pharmacokinetic

QbD	Quality by design
QD :	Once daily
QC	Quality control
QWP	Quality Working Party
QOS	Quality Overall Summary
QPD	Qualified Person Declaration
QTPP	Quality Target Product Profile
RH	Relative Humidity
RLD	Reference Listed Drug
RP	Restricted Part (or Closed Part) of an ASMF
RRT	Relative retention time
RSD	Relative standard deviation
RT	Retention Time
R	Reference product
SD	Standard deviation
SOP	Standard operating procedure
SmPC	Summary of Product Characteristics
SAS	Statistical software suite
tmax	Time to reach the maximum concentration of drug in plasma
t1/2	Elimination half-life/Plasma half-life
TAMC	Total Aerobic Microbial Count
TYMC	Total Yeast and Mould Count
T	Test product
TGF-β	Transforming growth factor-beta
Tmax	Time to maximum plasma concentration
TNF-α	Tumour necrosis factor-alpha
USAN	United States Adopted Name
UV	Ultraviolet
Vs	Versus
XRD	X-Ray Diffraction
yr	Year
λZ	The elimination rate constant

* This is a general list of abbreviations. Not all abbreviations will be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 6 February 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Dasatinib Accord Healthcare, 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 15 December 2022.

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 is or 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 Healthcare is indicated for the treatment of adult patients with:

- newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase.
- chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib.
- Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

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

- newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib.
- newly diagnosed Ph+ ALL in combination with chemotherapy.

1.2. Legal basis, dossier content

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.

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 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 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 tablet
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 20 November 2006
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number(s): EU/1/06/363/001-015
- Bioavailability study numbers: 0261-20 and 0262-20

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 submitted 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: Tomas Radimersky

The application was received by the EMA on	6 February 2023
The procedure started on	18 May 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	28 July 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	17 August 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 September 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 January 2024
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	23 February 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	7 March 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	21 March 2024
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	30 April 2024
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 May 2024
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 Healthcare on	30 May 2024
The CHMP adopted a report on similarity of Dasatinib Accord Healthcare with Scemblix, Iclusig, Tecartus, Blincyto, Besponsa and Kymriah on	30 May 2024

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.

Two bioequivalence studies were 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.

Dasatinib is an orally available small-molecule multitargeted kinase inhibitor. It potently inhibits BCR-ABL and SRC family kinases (SRC, LCK, YES, FYN) as well as c-KIT, PDGFR-α and β and ephrin receptor kinase at nanomolar concentrations. It has activity against most imatinib resistant isoforms of BCR-ABL. Dasatinib has been shown to block G1/S transition and inhibit cell growth in normal and neoplastic cells.

Proposed indications:

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

- newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase.
- chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib.
- Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

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

- newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib.
- newly diagnosed Ph+ ALL in combination with chemotherapy.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing dasatinib monohydrate equivalent to 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, 140 mg of dasatinib as active substance.

Other ingredients for the tablet core are: lactose monohydrate, cellulose, microcrystalline PH 101 (E460), croscarmellose sodium (E468), hydroxypropyl cellulose (E463), cellulose, microcrystalline PH 112 (E460), magnesium stearate (E470).

Other ingredients for the film-coating are: hypromellose (E464), titanium dioxide (E171), triacetin (E1518).

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

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of dasitinib monohydrate is N-(2-chloro-6-methylphenyl)-2-((6-(4-(2-hydroxyethyl) piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide monohydrate corresponding to the molecular formula $C_{22}H_{28}ClN_7O_3S$. It has a relative molecular weight of 506.02 and the following structure:

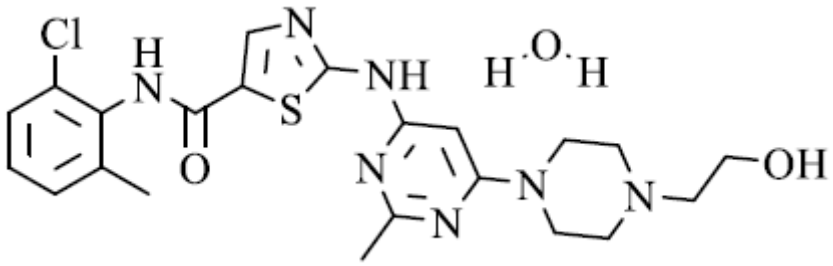

Figure 1: active substance structure

The chemical structure of dasatinib monohydrate was elucidated by a combination of elemental analysis, IR, UV, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy. The solid-state properties of the active substance were measured by DSC and XRD.

Dasatinib monohydrate is a white to off white powder. According to FDA BCS guideline, dasitinib is considered a low solubility active substance. It is very slightly soluble in acetone and acetonitrile, slightly soluble in ethanol, methanol, polyethylene glycol 400, propylene glycol and insoluble in corn oil. The active substance is non hygroscopic. It has a melting point about 288 °C.

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

Based on the literature survey, polymorphism has been observed for dasatinib monohydrate. The manufacturing process in Intas Pharmaceutical Limited, India consistently produces crystalline form of the active substance. Identity of the polymorphic form is tested at release and within the stability studies by XRD.

2.2.2.2. 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. A Major Objection (MO) was raised by CHMP related to the restricted part of the ASMF regarding the redefinition of one of the initially proposed starting materials used in the manufacture of the active substance. In their response the ASMF holder redefined the starting material to an earlier precursor and included relevant details of the synthesis. This was acceptable.

The detailed information about manufacturing process, yields at each step, quality of the starting materials, intermediates is included in the restricted part of the ASMF. The description of the manufacturing process given in the applicant's part of the ASMF has been updated in line with the starting material re-definition request.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, 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.

A detailed discussion supported by experimental studies has been provided for organic impurities. Carry-over analysis and spiking studies have been performed. In all cases, no impurities have been detected.

Information about the LoD and LOQ of each impurity has been provided. The impurity limits proposed in the intermediates and active substance specifications were tightened to reflect real batch data as requested by CHMP. The used standards of impurities of intermediates (origin, quality) have been satisfactorily discussed.

Dasatinib monohydrate is packaged in double transparent polyethylene bag and both polyethylene bags tied individually with tie seal. The polyethylene bags are placed in HDPE drum. The packaging material complies with EU directive 2002/72 and Ph. Eur.

2.2.2.3. Specification(s)

The active substance specification includes tests for description, solubility, identification (IR, HPLC), assay (HPLC), related substances (HPLC, GC), residual solvents (GC), water content (KF), sulphated ash (Ph. Eur.), polymorphic form (XRD), particle size (method) and microbial examination (TAMC, TYMC, E. Coli) (Ph. Eur.).

The active substance is not described in the Ph. Eur. The specification limits are established according to ICH and Ph. Eur. requirements. The impurity limits and the parameter concerning particle size and initially proposed non-routine testing of microbial quality have been reviewed during the procedure as requested by CHMP. The updated specification without skip testing of microbial purity has been presented.

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 for assay and impurities has been presented.

A risk assessment on the potential presence of nitrosamine impurities in the active substance has been provided. This has been supplemented by experimental data on three batches of AS, nitrosamines impurities are not detected.

The genotoxic impurities are discussed according to ICH M7. Considering the finished product indication the provided discussion is acceptable.

The residuals solvents are limited in line with ICH Q3C. All solvents used in the API synthesis are controlled in the active substance specification. Inorganic impurities are controlled by the sulphated ash. The limits for oral administration have been used. No suspicious trends occur.

Batch analysis data on 5 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

Stability data from four commercial scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 36 months under long term conditions (25 ºC / 60% RH) and for 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: description, identity (IR), water content (KF), related substances (HPLC, GC), assay (HPLC), polymorphic form (XRD) and microbial examination (Ph. Eur.). The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications.

The results of forced degradation studies under acid, alkali, oxidation, hydrolysis, thermal, UV and fluorescent light and humidity degradation have been provided. The peak purity has been demonstrated. No interference peak has been observed.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. It showed that the active substance is not light sensitive.

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 24 months without any special storage conditions in the proposed container.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

The finished product is presented as film-coated tablets in six strengths as described below. The different strengths of the finished product are differentiated by the size, shape and embossing differentiate the tablets, the colour of the tablets is the same (white to off-white).

Dasatinib 20 mg film-coated tablets

White to off-white, biconvex, approximate 5.5 mm round shaped, film-coated tablet debossed with "IV1" on one side & plain on the other side.

Dasatinib 50 mg film-coated tablets

White to off-white, biconvex, approximate 10.70 x 5.70 mm oval shaped, film-coated tablet debossed with "IV2" on one side & plain on the other side.

Dasatinib 70 mg film-coated tablets

White to off-white, biconvex, approximate 8.7 mm round shaped, film-coated tablet debossed with "IV3" on one side & plain on the other side.

Dasatinib 80 mg film-coated tablets

White to off-white, biconvex, approximate 10.20 x 9.95 mm triangular shaped, film-coated tablet debossed with"IV4" on one side & plain on the other side.

Dasatinib 100 mg film-coated tablets

White to off-white, biconvex, approximate 14.70 x 7.10 mm oval shaped, film-coated tablet debossed with "IV5" on one side & plain on the other side.

Dasatinib 140 mg film-coated tablets

White to off-white, biconvex, approximate 10.9 mm round shaped, film-coated tablet debossed with "IV6" on one side & plain on the other side.

The aim of the pharmaceutical development was to develop a generic dosage form of the reference medicinal product Sprycel 20 mg, 50 mg, 70 mg, 80 mg, 100 mg and 140 mg film-coated tablet, marketed by Bristol-Myers Squibb Pharma EEIG, Ireland.

For the development of Dasatinib film-coated tablets was traditional without Quality by Design (QbD) elements.

Dasatinib is a Biopharmaceutic Classification System (BCS) Class II active substance with low solubility. The following aspects were considered as part of the development of the generic formulation to mimic the reference product: the use of a micronized form of the active substance (due its low solubility), comparability of dissolution profiles of the test and reference products, the correct amount of the active substance in each tablet, acceptable characteristics of the tablets and product stability.

Excipients have been selected based on excipients used in the reference product Sprycel. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. Purified water is evaporated during processing and therefore it is not present in the final formulation. There are no novel excipients used in the finished product formulation.
The quantitative and qualitative composition for all tablet strengths is provided including details on the composition of the film-coating layer. There is dose proportionality of the excipients in the tablet cores as well as the core weights. The total weight of the coating layer is also proportional. No overage has been used. The list of excipients is included in section 6.1 of the SmPC.

Excipient concentrations and excipient grade quality were investigated. The effect of filler, binder and disintegrant on disintegration and dissolution was studied.

With regards to the selection of the manufacturing process for the tablets, direct compression was ruled out due to the poor flow of the active substance. A wet granulation approach with a scale up scale down strategy was chosen. The excipient compatibility studies with regards to the selected wet granulation process and functionality-related characteristics of excipients have been provided. The formulation does not show any incompatibility between the active substance and the proposed excipients. The stability data shows that the active substance and chosen excipients lead to a stable formulation.

All formulation trial steps have been adequately described. The initial development focused on the 100 mg and batch size of 1000 tablets. The other strengths were manufactured using the same formula, adjusting the composition in a quantitatively proportional manner for all strengths.

Testing parameters in the finished product specification justify the chosen formulation for the proposed route of administration.

Two bioequivalence studies were performed in order to demonstrate that the test product (Dasatinib film-coated tablets 140 mg) and the reference product (SPRYCEL Tablets 140 mg) are bioequivalent. For more information see clinical sections of the AR. In addition, comparative dissolution profiles of the test and reference products have been provided. These included a comparison of the dissolution profiles for the 140 mg test product and 140 mg reference product Sprycel, demonstrating similarity in different media.
Based on the acceptable bio-equivalence studies for Dasatinib 140 mg film-coated tablets, a request for waiver of BE study on the lower strengths i.e. 20 mg, 50 mg, 70 mg, 80 mg and 100 mg was requested and since the general requirements as per the *Guideline on the Investigation of Bioequivalence*, (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) are met, the strength biowaiver was accepted on the basis of in vitro data.
The dissolution method has been appropriately developed and the discriminatory power of the QC dissolution method has been demonstrated.

The primary packaging is blister pack (OPA/Alu/PVC//Alu). The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The manufacturing process consists of 10 main steps: raw material sifting, granulation, wet milling, drying, sizing, extra granular material sifting, blending, compression, film-coating, 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. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Critical steps were highlighted in the manufacturing process description. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

A range of batch sizes has been proposed for all strengths. The batch formula has been provided for at least the largest and smallest batch sizes in accordance with the Guideline on manufacture of the finished dosage form (EMA/CHMP/QWP/245074/2015).

No reprocessing of materials is allowed. Coating material is added in excess up to about 50% of the defined quantity to compensate possible loss during film-coating process.

The applicant confirmed that the Note for Guidance on Start of shelf-life of the finished dosage form is applied (CPMP/QWP/072/96), i.e., shelf-life starts upon combining the active substance with other ingredients.

Details of hold time study for one batch are provided for film-coated tablet of Dasatinib 20 mg (). Tablets were held in double polyethylene bag in HDPE container used for routine manufacturing for a. Based on satisfactory results, hold time is proposed for film-coated tablets. The applicant has provided a commitment to perform a suitable hold time study on at two production batches of selected strengths to support the holding time of the drug product according to the approved specifications.

2.2.3.3. Product specification(s)

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: description, average weight of tablet, identification (UV, HPLC), water content (by KF), dissolution (UV), related substances (HPLC), uniformity of dosage units (content uniformity, HPLC), assay (HPLC) and microbial examination (TAMC, TYMC, E. Coli) (Ph. Eur.). The specifications below apply to all strengths of the finished product.

The specification tests and limits were set in line with relevant ICH guidelines, Ph. Eur. Requirements and batch data.

With regard to the dissolution limit the CHMP raised a MO asking the applicant to tighten the specification limit for dissolution in line with the provided dissolution data of the biobatch as per *Reflection paper on the dissolution specification for generic oral immediate release products with systemic action* (EMA/CHMP/CVMP/QWP/336031/2017). The MO was satisfactorily resolved by tightening the dissolution limit of the finished product.

The method used to determine the water content has been discussed. Satisfactory CoAs for batches of all strengths have been provided, all parameters are within the limits, results indicate that the process is under control.
The limits for water content and total degradation products were also tightened. Limits for two known impurities were tightened in line with ICH Q3B (R2) (CPMP/ICH/2738/99).

The test of microbial control is performed for first five batches followed by every fifth batch or one batch per year, whichever is earlier.

The possible genotoxic impurities are sufficiently discussed according to ICH M7. Considering the finished product indication the provided discussion is acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Each relevant elemental impurity was not detected above 30% of the respective PDE. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) 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 there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific 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 for assay and impurities has been presented. The stability indicating nature of the HPLC method used for determination of related substances and assay has been demonstrated.

Batch analysis results are provided for three production scale batches for each strength of Dasatinib 20/50/70/80/100/140 mg film-coated tablets confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.2.3.4. Stability of the product

Stability data from three production scale batches from each strength of dasatinib 20/50/70/80/100/140 mg film-coated tablets stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 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 in accordance with the shelf-life specification for 20 mg, 50 mg, 70 mg, 80 mg, 100 mg and 140 mg. The following is tested: description, average weight of tablet, identification (UV, HPLC), water content (by KF), dissolution (UV), related substances (HPLC), uniformity of dosage units (content uniformity, HPLC), assay (HPLC) and microbial examination (TAMC, TYMC, E. Coli) (Ph. Eur.). The analytical procedures used are stability indicating.

At long term and accelerated conditions, the results remained within the specification limits and no significant trend was observed.

For the post-approval stability study program, a bracketing approach has been proposed in accordance with ICH Q1D *Bracketing and matrixing designs for stability testing of drug substances and drug products.* This is acceptable.

In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

In addition, a photostability study was conducted on Dasatinib 20 mg and 140 mg film-coated tablets as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The Dasatinib film-coated tablets are found to be photostable.

Based on available stability data, the proposed shelf-life of 24 months without any special storage conditions as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

2.2.3.5. 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.

Two MOs were raised during the procedure. The first MO related to the redefinition of one of the originally proposed starting materials for the active substance (Restricted part of the ASMF). The second MO requested the applicant to tighten the QC dissolution limit of the finished product in line with the biobatch performance. The MOs were satisfactorily resolved by redefining the starting material of the active substance and tightening the dissolution limit of the finished product, as requested.

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.

At the time of the CHMP opinion, there was a minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to the hold time of film-coated tablets. These points are 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.

2.2.6. Recommendation(s) 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 perform a hold time study on two commercial batches of Dasatinib tablets by following the applicable guidelines to support the holding time.

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

The submitted environmental risk assessment consisted of a Phase I exposure assessment. Since the refined PECsw value was below 0.01 µg/L, and no other environmental concerns were apparent, it is concluded that the medicinal product Dasatinib Accord Healthcare 20, 50, 70, 80, 100, and 140 mg film-coated tablets is unlikely to present a risk for the environment following its prescribed usage in patients.

2.3.3. Discussion on non-clinical aspects

The CHMP considers that the non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. The proposed specification limits for drug related impurities in drug product are below qualification threshold following the provided responses.

2.3.4. Conclusion on the non-clinical aspects

Dasatinib Accord Healthcare is approvable 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

To support the marketing authorisation application the applicant conducted 2 bioequivalence studies with cross-over design under fasting and fed conditions. These 2 studies were the pivotal studies for this application.

In addition, the applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of dasatinib based on published literature.

No scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

GCP aspect

The Clinical trial was 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 2 bioequivalence studies in support of this application, and these were 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 i.e. 20 mg, 50 mg, 70 mg, 80 mg, 100 mg and 140 mg of proposed pharmaceutical product are manufactured by the same manufacturing process.

- The qualitative composition of Dasatinib film-coated tablets 20 mg, 50 mg, 70 mg, 80 mg and 100 mg is the same as that of Dasatinib film-coated tablets 140 mg.

- The composition of all strengths is quantitatively proportional, i.e. the ratio between the amounts of each excipient to the amount of active substance is the same for all strengths.

- The in vitro dissolution profile is similar under identical conditions for the additional strengths i.e. 20 mg, 50 mg, 70 mg, 80 mg, 100 mg and the strength of batch used in the bioequivalence study i.e. 140 mg.

- Dasatinib film-coated tablets exhibits linear pharmacokinetics.

Tabular overview of clinical studies

To support the application, the applicant has submitted the following two bioequivalence studies.

Type of study	Study Identifier	Location of Study Report	Objective(s) of the study	Study design and Type of Control	Test Product(s); Dosage Regimen; Route of administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	0261-20	• m5-3-1-2-vol 1 of 4 • m5-3-1-2-vol 2 of 4 • m5-3-1-2-vol 3 of 4 • m5-3-1-2-vol 4 of 4	An open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, crossover, fully replicate, bioequivalence study of dasatinib tablets 140 mg in normal, healthy, adult, human subjects under fasting condition	Four-period, two-sequence, single oral dose, crossover, fully replicate, bioequivalence study, fasting condition	Dasatinib Tablets 140 mg, Single dose, Oral	90	Healthy, Adult, Human subjects	Single dose	Complete; Full
BE	0262-20	• m5-3-1-2-vol 1 of 4 • m5-3-1-2-vol 2 of 4 • m5-3-1-2-vol 3 of 4 • m5-3-1-2-vol 4 of 4	An open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, crossover, fully replicate, bioequivalence study of dasatinib tablets 140 mg in normal, healthy, adult, human subjects under fed condition	Four-period, two-sequence, single oral dose, crossover, fully replicate, bioequivalence study, fed condition	Dasatinib Tablets 140 mg, Single dose, Oral	40	Healthy, Adult, Human subjects	Single dose	Complete; Full

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study 0261-20: An open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, crossover, fully replicate, bioequivalence study of dasatinib tablets 140 mg in normal, healthy, adult, human subjects under fasting condition.

Table 1 - Summary of study information

Study Site (clinical, analytical, statistical):	Lambda Therapeutic Research Ltd., India.
Sponsor:	Intas Pharmaceuticals Ltd., India
Clinical Phase Dates:	19 June 2021 – 07 July 2021
Bioanalytical Phase Dates:	16 July 2021 – 10 August 2021
Date of the Clinical Study Report:	31 August 2021
Date of the Bioanalytical Report:	31 August 2021
Date of the Method Validation Report	10 March 2017 (Addendum-IV: 24 July 2021)

Methods

- **Study design**

This was an open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, crossover, fully replicate, bioequivalence study of dasatinib tablets 140 mg in normal, healthy, adult, human subjects under fasting condition.

Primary objective was to compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's test product relative to that of reference product after single oral dose administration in normal, healthy, adult, human subjects under fasting condition and to assess the bioequivalence.

Secondary objective was to monitor the safety of the subjects.

After an overnight fast of at least 10 hours, a single oral dose (140 mg) of either the test product or the reference product was administered to the subjects while in sitting position with 240 ± 2 mL of drinking water at ambient temperature. The IMP administration was as per the randomisation schedule and under open label conditions.

The tablet was swallowed whole without chewing or crushing.

Subjects refrained from drinking water from 1 hour before till 1 hour after each dosing in each period except for water administered during dosing. Prior to and thereafter, water was consumed as required.

A total of twenty-six (26) blood samples, were to be collected from each subject in each period. The venous blood samples were withdrawn at pre-dose (0.000 hour) and at 0.167, 0.333, 0.500, 0.750, 1.000, 1.333, 1.667, 2.000, 2.333, 2.667, 3.000, 3.333, 3.667, 4.000, 4.500, 5.000, 6.000, 7.000, 8.000, 10.000, 12.000, 16.000, 20.000, 24.000 and 36.000 hours following IMP administration in each period.

The plasma samples of subjects were analysed by a validated LC-MS/MS method.

A washout period of 4 days was maintained between the dosing days of any two consecutive periods

Protocol deviations

Table 2. Protocol deviations Study 0261-20

<table>
<tr><th>Period</th><th>Type of deviation</th><th colspan="3">Deviation details</th></tr>
<tr><td rowspan="3">II</td><td rowspan="3">Pre-dose Housing</td><td colspan="3">As per the protocol, subjects were to be housed in the clinical facility at least 36 hours before administration of the IMP in each period.
However, deviations were observed in this regards as the subject came late. Details are as below:</td></tr>
<tr><td>Scheduled time (hh:mm)</td><td>Actual time (hh:mm)</td><td>Deviation without window period (in minutes)</td></tr>
<tr><td>20:30</td><td>21:07</td><td>37</td></tr>
<tr><td>I to IV</td><td>Temperature Recording</td><td colspan="3">As per the protocol, oral body temperature was to be recorded at screening, after check-in and before check-out in each period for all the subjects.
However, as a preventive safety measure and a step to avoid spread of coronavirus diseases considering prevailing COVID-19 pandemic, it was planned that instead of oral body temperature, axillary body temperature was performed for all the subjects.</td></tr>
</table>

Concomitant therapy

Few subjects were administered medicines to treat their adverse events.

- **Test and reference products**

Dasatinib Tablets 140 mg manufactured by Intas Pharmaceuticals Ltd, India (batch No.P20005884, exp. date 31 October 2022) has been compared to SPRYCEL (dasatinib) tablets 140 mg manufactured by Bristol-Myers Squibb S.r.l, Italy (Lot No: ABN4602, exp. date 31 October 2022).

- **Population(s) studied**

89 healthy adult male human subjects were enrolled. The study started with 89 subjects and 69 completed the study.

Table 3. Number of subjects (planned and analysed) Study 0261-20

Number of subjects (planned and analysed):

Planned for inclusion			90
Pre-dose Discontinued			03
Dosed	Group-I	Period-I	39
		Period-II	34
		Period-III	33
		Period-IV	30
	Group-II	Period-I	50
		Period-II	47
		Period-III	44
		Period-IV	47
Post-dose Discontinued/Withdrawn			20
Analysed			89
Considered for statistical analysis			84

No female volunteers were checked in for the study. The race of the subjects was specified as Asians.

Table 4. Demographic and other baseline characteristics, Study 0261-20

Parameter (Units)	Mean ± SD	
	N = 89 (Dosed Subjects)	N=84 (Subjects included in BE evaluation)
Age (years)	31.9 ± 5.77	31.9 ± 5.86
Height (cm)	166.66 ± 6.370	166.81 ± 6.495
Weight (kg)	63.853 ± 10.4116	63.940 ± 10.5349
BMI (kg / m^2)	22.942 ± 3.1210	22.927 ± 3.1081

No female volunteers were checked in for the study. The race of the subjects was specified as Asians.

Randomization

The order of receiving test product and reference product for each subject in each period of the study was determined according to the randomization schedule. Equal allocation of subjects to each treatment sequence was ensured.

Blinding

This was an open label study; hence blinding was not done. However, the analysts performing the assay of the drug in plasma were unaware of the sequence of administration of reference product and test product to the individual subjects.

- **Analytical methods**

The plasma concentrations of dasatinib in the study samples were determined by a validated LC MS/MS method using dasatinib-d8 as the internal standard. The analyte and internal standard were extracted from human plasma using solid-phase extraction method. The method was validated over the calibration curve range from 1.021 ng/mL to 500.158 ng/mL.

The blood samples were obtained using blood collection tubes containing K2EDTA as the anticoagulant. The blood samples were kept in ice cold water bath until centrifugation for precaution purpose. The blood samples were centrifuged at 3000 rcf for 5 minutes at 3°C. The samples were stored upright in a freezer at a temperature between -71.94°C and -54.88 °C for interim storage till transfer to the bio-analytical department. The samples were received by bioanalytical facility in frozen condition in boxes containing adequate amount of dry ice and were transferred to the freezer and stored within the temperature range of -73.53°C to -52.16 °C until completion of analysis.

Calibration curve standards and quality control samples prepared during method validation were also used. Separately weighed stocks were used for the preparation of calibration curve standards and quality control samples. Calibration curve standards and quality control samples were stored in the freezer maintained at -65 ± 10°C. Number of QC samples was at least 5% of the number of unknown samples (16, four at each concentration level). At least two QC levels were representative of the observed concentrations in the study samples.

The in-study data of back-calculated calibration standards and between-run QC samples accuracy and precision demonstrated reliable performance of the method during analyses of study samples. All analytical run acceptance criteria followed the Guideline on Bioanalytical Method Validation.

Bioanalytical method validation

A LC-MS/MS method for the estimation of dasatinib in human plasma has been developed and validated in 2017. The method was partially validated for change in extraction solvent, buffer, injection volume and for change in reconstitution solvent, column, mobile phase etc.

- **Pharmacokinetic variables**

Primary pharmacokinetic parameters: Cmax, AUC0-t

Secondary pharmacokinetic parameters: AUC0-∞, Tmax, Terminal half-life (t1/2), λz, AUC_%Extrap_obs

Actual time-points of sample collection were used for the calculation of pharmacokinetic parameters. All concentration values below the lower limit of quantification were set to zero for the pharmacokinetic and statistical calculations.

- **Statistical methods**

Descriptive statistics were calculated and reported for the pharmacokinetic parameters of dasatinib.

Descriptive statistics and statistical analysis were performed on subjects having pharmacokinetic parameters available for at-least two treatment periods; one with test product and other with reference product.

The ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were subjected to analysis of variance (ANOVA) for dasatinib.

As study was conducted in multiple groups, ANOVA model included group, sequence, sequence*group, subject (sequence*group), formulation, period (group) as fixed effects. Each analysis of variance included calculation of least-squares means, the difference between adjusted formulation means and the standard error associated with this difference.

If number of subjects for BE evaluation was < 5 subjects in any group, then that group was combined to another group.

An F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (alpha = 0.05).

Ratio of geometric least-squares means of test and reference formulations was calculated and reported for the ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for dasatinib.

The within subject standard deviation (S_{WR}) of reference product and intra-subject variability of reference product was calculated and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for dasatinib.

Any missing samples (M) or non-reportable (NR) concentration values were disregarded in pharmacokinetic and statistical analysis.

90% confidence intervals for the ratio of geometric least squares means between drug formulations were calculated for ln-transformed data of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for dasatinib.

Criteria for conclusion of bioequivalence were as follows:

Bioequivalence of test product vs. reference product was concluded, if the 90% confidence interval for the ratio of the geometric least squares means fell within the acceptance range as defined below for ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for dasatinib with following consideration.

1. For AUC_{0-t}:

If the 90% confidence interval of geometric least squares means ratio of test to reference fell within the acceptance range of 80-125% for ln-transformed pharmacokinetic parameter AUC_{0-t}.

- For Cmax:

1. If within-reference intra-subject CV of ln-transformed pharmacokinetic parameter $C_{max} \leq 30\%$ then bioequivalence of the test product with that of the reference product was to be concluded, if the 90% confidence interval fell within the acceptance range of 80-125% for ln-transformed pharmacokinetic parameter C_{max} for dasatinib.

2. If within-reference intra-subject CV of ln-transformed pharmacokinetic parameter $C_{max} > 30\%$ then C_{max} limit was to be widened using scaled-average bioequivalence. Under scaled-average bioequivalence, $[U, L] = \exp [\pm k \cdot S_{WR}]$, where U is the upper limit of the acceptance range, L is the lower limit of the acceptance range, k is the regulatory constant set to 0.760 and S_{WR} is the within-subject standard deviation of the ln-transformed values of C_{max} of the reference product.

3. If within-reference intra-subject CV of ln-transformed $C_{max} \geq 50\%$ then C_{max} limit was to be widen maximum up to 69.84 to 143.19%.

Bioequivalence of the test product with that of the reference product was concluded for C_{max} of dasatinib, if both of the following conditions were satisfied:

- The 90% confidence interval for ln-transformed data of C_{max} fell within the newly widened acceptance range $[U, L] = \exp [\pm k \cdot S_{WR}]$, which was to be based upon the within-subject variability of reference product observed for C_{max}.

- The geometric least square mean ratio (GMR) of test to reference for C_{max} fell within the acceptance range of 80-125%.

Results

Ninety (90) subjects were planned into the study, however, only 89 subjects were enrolled, of which 69 subjects completed all the periods of clinical phase of the study. Amongst the withdrawn subjects, 15 subjects completed at-least two treatment periods with one reference and one test formulation. Hence, all completer's subjects along with these fifteen subjects were included in the calculation of pharmacokinetic and statistical analysis, so 84 subjects were included in PK and statistical analysis of dasatinib.

Thirteen subjects withdrew on medical grounds. Five subjects discontinued on their own accord.

Table 5. Pharmacokinetic parameters for dasatinib (non-transformed values)

Pharmacokinetic parameter	**Test (N = 158)**		**Reference (N = 158)**	
	arithmetic mean	**SD**	**arithmetic mean**	**SD**
$AUC_{(0-t)}$ (ng.h/mL)	1095.88	472.63	1055.10	467.14
$AUC_{(0-\infty)}$ (ng.h/mL)$^{\$}$	1124.97	466.33	1085.02	458.52
C_{max} (ng/mL)	274.54	141.05	264.51	143.96
T_{max}* (h)	1.33	(0.50-16.00)	1.33	(0.50-24.00)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to 36 hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			
N	number of observations			

$ For $AUC_{0-\infty}$ number of observations N = 157 for Test and Reference

Table 6. Statistical analysis for dasatinib (ln-transformed values)

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Reference**	**Confidence Intervals**	**CV% of reference product***
$AUC_{(0-t)}$	104.3	92.69-117.30	61.1
C_{max}	106.0	90.19-124.57	92.3
* estimated from the Residual Mean Squares			

Group, sequence*group, formulation and period(group) effects were found to be statistically insignificant for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for dasatinib.

Sequence effect was found to be statistically significant for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for dasatinib.

The cause for significant sequence effect may not be found with certainty. Therefore, under special circumstances the significant sequence effect can be ignored. The study [1] was a single dose study [2] was in healthy volunteers, [3] was not comparing an endogenous substance, [4] had an adequate washout and [5] used appropriate design and analysis. Hence, this sequence effect was just statistically significant and can be ignored.

Subject(sequence*group) effect was found to be statistically significant for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for dasatinib.

Since each subject was assigned only one sequence within the group, subjects were said to be nested within sequence*group. This subject(sequence*group) effect was tested by the residual and should be highly significant. This significance was an indication that the purpose of using the crossover design has been realized in that the between-subject variance was significantly larger than the residual.

The results of this study demonstrated that the criteria used to assess bioequivalence between the test and reference formulations were fulfilled.

The 90% CI of geometric least square means ratio of test to reference was within the acceptance range of 80 to 125% for ln-transformed pharmacokinetic parameter AUC_{0-t} for dasatinib.

The 90% CI for ln-transformed pharmacokinetic parameter C_{max} was within the newly widen range of 69.84 – 143.19% for dasatinib.

The geometric least-square means ratio (GMR) of test to reference for ln-transformed pharmacokinetic parameter C_{max} was within the acceptance range of 80 to 125% for dasatinib.

- **Safety data**

The safety assessment includes information for all 89 subjects who were dosed at least once during this study.

Seventeen (17) adverse events (AEs) were reported by fifteen (15) subjects during the conduct of the study. One (1) AE was reported in Period-I, five (05) AEs were reported in Period-II, eight (8) AEs were reported in Period-III and three (3) AEs were reported in Period-IV of the study.

Eleven (11) AEs were reported in the subjects after administration of Test Product-T and six (6) AEs were reported in the subjects after administration of Reference Product-R.

All AEs were mild in nature. The subjects were followed up until resolution of their AEs.

The causality assessment was judged, as possible for twelve (12) AEs, as unlikely for four (4) AEs and as unrelated for one (1) AE.

There were no deaths or serious AEs reported during the conduct of the study.

However, out of the total reported seventeen (17) AEs, fifteen (15) AEs were significant. The subjects were withdrawn on medical grounds. They were treated appropriately and followed up until resolution of their AEs. The causality assessment was judged as unlikely for four (4) AEs, as possible for ten (10) AEs and as unrelated for one (1) AE.

Study 0262-20: An open label, balanced, randomized, two treatment, four-period, two-sequence, single oral dose, crossover, fully replicate, bioequivalence study of dasatinib tablets 140 mg in normal, healthy, adult, human subjects under fed condition.

Table 7. Summary of study information

Study Site (clinical, analytical, statistical)	Lambda Therapeutic Research Ltd., India.
Sponsor:	Intas Pharmaceuticals Ltd., India
Clinical Phase Dates:	17 June 2021 – 02 July 2021
Bioanalytical Phase Dates:	09 July 2021 – 20 July 2021
Date of the Clinical Study Report:	31 August 2021
Date of the Bioanalytical Report:	31 August 2021
Date of the Method Validation Report	10 March 2017 (Addendum-IV: 24 July 2021)

Methods

- **Study design**

  This was an open label, balanced, randomized, two treatment, four-period, two-sequence, single oral dose, crossover, fully replicate, bioequivalence study of dasatinib tablets 140 mg in normal, healthy, adult, human subjects under fed condition.

Primary objective was to compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's test product relative to that of reference product after single oral dose administration in normal, healthy, adult, human subjects under fed condition and to assess the bioequivalence.

Secondary objective was to monitor the safety of the subjects.

After an overnight fast of at least 10 hours, the subjects were served high fat high calorie vegetarian breakfast, which they consumed completely within 30 minutes.

A single oral dose (140 mg) of either the test product or the reference product was administered to the subjects at 30 minutes after serving the breakfast. The IMP was administered in sitting posture with 240 ± 02 mL of drinking water at ambient temperature. The IMP administration was as per the randomization schedule and under open label conditions.

The tablet was swallowed as whole without chewing or crushing.

Subjects refrained from drinking water from 1 hour before till 1 hour after each dosing in each period except for water administered during dosing. Prior to and thereafter, water was consumed as required.

Total of twenty-seven (27) blood samples, each of 3 mL were to be collected from each subject in each period. The venous blood samples were withdrawn at pre-dose (0.000 hour) and at 0.167, 0.333, 0.500, 0.750, 1.000, 1.333, 1.667, 2.000, 2.333, 2.667, 3.000, 3.333, 3.667, 4.000, 4.500, 5.000, 5.500, 6.000, 7.000, 8.000, 10.000, 12.000, 16.000, 20.000, 24.000 and 36.000 hours following IMP administration in each period.

The plasma samples of subjects were analysed by a validated LC-MS/MS method.

A washout period of 4 days was maintained between the dosing days of any two consecutive periods.

Protocol deviations

Table 8. Protocol deviations Study 0262-20

Period	Type of deviation	Deviation details
I to IV	Temperature Recording	As per the protocol, oral body temperature was to be recorded at screening, after check-in and before check-out in each period for all the subjects. However, as a preventive safety measure and a step to avoid spread of coronavirus diseases considering prevailing COVID-19 pandemic, it was planned that instead of oral body temperature, axillary body temperature was performed for all the subjects.
End-Study	Post-study assessment	As per the protocol, a clinical examination including recording of vital signs and body temperature and laboratory tests for hematology and biochemistry (except random glucose, sodium, potassium and chloride) of the subjects were to be conducted at the end of the study (at the time of check-out of Period-IV). However, the same was not performed for the subjects, they were contacted telephonically and asked to visit to report for post-study. However, they did not report to the clinical facility and they were considered as lost to follow-up.

Concomitant therapy

Few subjects were administered medicines to treat their adverse events.

- **Test and reference products**

Dasatinib Tablets 140 mg manufactured by Intas Pharmaceuticals Ltd, India (batch No.P20005884, exp. date 31 October 2022) has been compared to SPRYCEL (dasatinib) tablets 140 mg manufactured by Bristol-Myers Squibb S.r.l, Italy (Lot No: ABN4602, exp. date 31 October 2022).

- **Population studied**

Table 9. Number of subjects (planned and analysed), Study 0262-20

Planned for inclusion		40
Pre-dose discontinued / withdrawn		00
Dosed	Period-I	40
	Period-II	33
	Period-III	31
	Period-IV	30
Post-dose discontinued/withdrawn		15
Analysed		40
Considered for statistical analysis		35

No female volunteers were checked in for the study. The race of the subjects was specified as Asians.

Randomization

The order of receiving the test and reference products for each subject during all the periods of the study was determined according to a randomization schedule. Equal allocation of subjects to each treatment sequence was ensured.

Blinding

This was an open label study; hence blinding was not done. However, the analysts performing the assay of the drug in plasma were unaware of the sequence of administration of reference product and test product to the individual subjects.

- **Analytical methods**

For detailed evaluation of analytical methods, please see the study 0261-20 section "Analytical methods" above.

- **Pharmacokinetic variables**

  - Primary pharmacokinetic parameters: Cmax, AUC0-t
  - Secondary pharmacokinetic parameters: AUC0-∞, Tmax, Terminal half-life (t1/2), λz, AUC_%Extrap_obs

Actual time-points of sample collection were used for the calculation of pharmacokinetic parameters. All concentration values below the lower limit of quantification were set to zero for the pharmacokinetic and statistical calculations.

- **Statistical methods**

For detailed description of statistical methods, please see the study 0261-20 section "Statistical methods" above.

Results

Forty (40) subjects were planned and enrolled into the study of which 25 subjects completed all the periods of clinical phase of the study. Amongst the withdrawn subjects, 10 subjects completed at-least two treatment periods with one reference and one test formulation. Hence, all completer's subjects along with these ten subjects were included in the calculation of pharmacokinetic and statistical analysis, so 35 subjects were included in PK and statistical analysis of dasatinib.

Ten (10) subjects withdrawn on medical grounds. Four (4) subjects discontinued on their own accord.

Table 10 - Pharmacokinetic parameters for Dasatinib (non-transformed values)

Pharmacokinetic parameter	**Test (N = 62)**		**Reference (N = 65)**	
	arithmetic mean	**SD**	**arithmetic mean**	**SD**
$AUC_{(0-t)}$ (ng.h/mL)	1163.43	303.34	1132.35	290.17
$AUC_{(0-\infty)}$ (ng.h/mL)	1184.59	309.34	1152.71	289.39
C_{max} (ng/mL)	210.51	62.61	205.08	55.11
T_{max}* (h)	3.33	(0.75-6.00)	3.67	(1.00-6.00)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to 36 hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			
N	number of observations			

Table 11 - Statistical analysis for Dasatinib (ln-transformed values)

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Reference**	**Confidence Intervals**	**CV% of reference product***
$AUC_{(0-t)}$	100.4	95.26-105.73	12.6
C_{max}	98.8	91.90-106.32	16.4
* estimated from the Residual Mean Squares			

Formulation and sequence effects were found to be statistically insignificant for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for dasatinib.

Period and subject (sequence) effects were found to be statistically significant for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for dasatinib. In this study, clinical conditions were kept identical in all the period of the study, and there were no pre-dose concentrations observed. Further, study met all the bioequivalence criteria as defined in the protocol. This significant period effect for ln-transformed pharmacokinetic parameter C_{max} is just statistically significant and can be ignored. Since each subject is assigned only one sequence, subjects are said to be nested within sequence. This subject (sequence) effect is tested by the residual and should be highly significant. This significance is an

indication that the purpose of using the crossover design has been realized in that the between-subject variance is significantly larger than the residual.

- ***Safety data***

Fifteen (15) adverse events (AEs) were reported by twelve (12) subjects during the conduct of the study. Four (4) AEs were reported in Period-II, six (6) AEs were reported in Period-III, four (4) AEs were reported in Period-IV and one (01) AE was reported during post-study safety assessment.

Nine (9) AEs were reported in the subjects after administration of Test Product-T and six (6) AEs were reported in the subjects after administration of Reference Product-R.

All the AEs were mild in nature. The subjects were followed up until resolution of their AEs.

The causality assessment was judged as unlikely for five (05) AEs and as possible for ten (10) AEs.

There were no deaths or serious AEs reported during the conduct of the study.

However, out of the total reported fifteen (15) AEs, ten (10) AEs were significant. The subjects were withdrawn on medical grounds. They were treated appropriately and followed up until resolution of their AEs. The causality assessment was judged as unlikely for four (4) AEs and as possible for six (6) AEs.

2.4.2.2. Pharmacodynamics

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

2.4.3. Discussion on clinical aspects

To support the application, the applicant has submitted two bioequivalence studies.

Bioequivalence study No. 0261-20: An open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, crossover, fully replicate, bioequivalence study of dasatinib tablets 140 mg in normal, healthy, adult, human subjects under fasting condition.

Bioequivalence study No. 0262-20: An open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, crossover, fully replicate, bioequivalence study of dasatinib tablets 140 mg in normal, healthy, adult, human subjects under fed condition.

Based on the presented bioequivalence studies, Dasatinib 140 mg film-coated tablet is considered bioequivalent with Sprycel 140 mg film-coated tablet, since the test product when compared with the reference product meets the bioequivalence criteria with respect to C_{max} and AUC_{0-t} for dasatinib under fasting and fed conditions as per criteria.

Based on the acceptable bioequivalence studies for Dasatinib 140 mg film-coated tablets, a request for a waiver to perform bioequivalence studies on the lower strengths i.e. 20 mg, 50 mg, 70 mg, 80 mg and 100 mg was requested by the applicant. Since the general requirements as per the *Guideline on the Investigation of Bioequivalence*, (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) are met, the strength biowaiver was accepted on the basis of in vitro data.

Therefore, the results of the bioequivalence studies performed on the 140mg strength can be extrapolated to other strengths (20mg, 50mg, 70mg, 80mg, and 100mg), according to conditions in the relevant Guidelines. Please refer to the quality sections for further information.

The SmPC is in line with the SmPC of the reference product.

2.4.4. Conclusions on clinical aspects

The product is approvable from a clinical point of view.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns	
Important identified risks	Myelosuppression Fluid retention Bleeding related events QT prolongation Pulmonary Arterial Hypertension (PAH) Pregnancy related malformative or foeto/ neonatal toxicity Nephrotic Syndrome Thrombotic Microangiopathy
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
Missing information	Carcinogenicity Paediatric data: Children < 1 year of age Reproductive and lactation data

2.5.2. Pharmacovigilance plan

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in the pharmacovigilance system master file are sufficient for this medicinal product.

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

The safety information in the proposed Product Information is aligned to the reference medicinal product.

No additional risk minimisation measures are required.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 is acceptable. The RMP is aligned with the originator product (Sprycel).

The applicant is reminded that the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

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

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Sprycel. The bridging report submitted by the applicant has been found acceptable.

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:

- newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase.
- chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib.
- Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

And the treatment of paediatric patients with:

- newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib.
- 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.

Two bioequivalence studies form the pivotal basis with an open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, crossover, fully replicate designs. 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 Healthcare 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 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 Healthcare is not similar to Scemblix, Iclusig, Tecartus, Blincyto, Besponsa 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 Healthcare is favourable in the following indication:

For the treatment of adult patients with:

- newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase.
- chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib.
- Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

And for the treatment of paediatric patients with:

- newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib.
- 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.