25 July 2024
EMA/372021/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Axitinib Accord

International non-proprietary name: axitinib

Procedure No. EMEA/H/C/006206/0000

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

%	Percentage
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
avF	Arteriovenous fistula
ccRCC	clear cell RCC
chRCC	chromophobe RCC
CI	Confidence Intervals
C_{max}	The maximum concentration
COVID-19	Corona Virus Disease 2019
CYP	Cytochromes P450
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
Erk	Extracellular signal-regulated kinases
GCP	Good Clinical Practice
GMR	Geometric mean ratio
hr	Hour
HR	Hazard Ratio
ITT	Intent-to-treat
K_{el}	Elimination Rate Constant
MAA	Marketing authorization application
MRI	Magnetic resonance image
mTOR	Mammalian target of rapamycin
NE	Not estimable
NS	Not statistically significant
N_{WR}:	Number of Subjects used for SWR calculation
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PDGF	Platelet-derived growth factor
PFS	Progression-free survival
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PPE	Palmar-plantar erythrodysaesthesia
pRCC	papillary RCC
PRES	Posterior reversible encephalopathy syndrome
PT	Prothrombin time
R	Reference product

Raf	Rapidly accelerated fibrosarcoma
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
S6K1	Ribosomal protein S6 kinase beta-1
SD	Standard deviation
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SmPC	Summary of product characteristics
S_{WR}	Within-subject standard deviation of the reference product
T	Test product
$t_{1/2}$	Half life
T3	Triiodothyronine
T4	Thyroxine
t_{max}	The time take to reach C_{max}
TSH	Thyroid-stimulating hormone.
ULN	Upper limit of normal
uRCC	unclassified RCC
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptors

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 6 March 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Axitinib 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 13 October 2022.

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 Inlyta instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is: Inlyta.

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: Inlyta, 1mg, 3mg, 5mg, 7mg, film-coated tablets
- Marketing authorisation holder: Pfizer Europe MA EEIG
- Date of authorisation: 03-09-2012
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number:
- 1mg - EU/1/12/777/001-003
- 3mg - EU/1/12/777/007-009
- 5mg - EU/1/12/777/004-006
- 7mg - EU/1/12/777/010-012

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

- Product name, strength, pharmaceutical form: Inlyta, 1mg, 3mg, 5mg, 7mg, film-coated tablet
- Marketing authorisation holder: Pfizer Europe MA EEIG
- Date of authorisation: 03-09-2012
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number:
- 1mg - EU/1/12/777/001-003
- 3mg - EU/1/12/777/007-009

- 5mg - EU/1/12/777/004-006
- 7mg - EU/1/12/777/010-012

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: Inlyta, 5mg, film-coated tablet
- Marketing authorisation holder: Pfizer Europe MA EEIG
- Date of authorisation: 03-09-2012
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number(s): EU/1/12/777/004-006
- Bioavailability study number(s): 054-21

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 not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4.2. Derogation(s) from market exclusivity

N/A

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 were: Ewa Balkowiec Iskra.

The application was received by the EMA on	6 March 2023
The procedure started on	23 March 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 June 2023
The PRAC Rapporteur's first Assessment Report was circulated to all	26 June 2023

PRAC and CHMP members on	
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 July 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 February 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	2 April 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N.A
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	25 April 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	28 May 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	20 June 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	27 June 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	2 July 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	18 July 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 Axitinib Accord on	25 July 2024

2. Scientific discussion

2.1. Introduction

This marketing authorisation application (MAA) is for a generic medicinal product; Axitinib 1mg, 3mg, 5 mg, 7 mg, film-coated tablets containing the same active substance as the approved reference product Inlyta (axitinib) film-coated tablets 1mg, 3mg, 5 mg and 7 mg of Pfizer Europe. One BE study was submitted to support this MAA with the 5 mg strength.

Axitinib is a potent and selective tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2 and VEGFR-3. These receptors are implicated in pathologic angiogenesis, tumour growth, and metastatic progression of cancer. Axitinib has been shown to potently inhibit VEGF-mediated endothelial cell proliferation and survival. Axitinib inhibited the phosphorylation of VEGFR-2 in xenograft tumour vasculature that expressed the target in vivo and produced tumour growth delay, regression, and inhibition of metastases in many experimental models of cancer.

The reference product Inlyta is currently authorised for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 1 mg, 3 mg or 5mg of axitinib as active substance.

Other ingredients are:

Tablet core: lactose anhydrous, cellulose microcrystalline (E460), silica colloidal anhydrous, hydroxypropyl cellulose (300–600 mPa*s), croscarmellose sodium (E 468), talc, magnesium stearate (E 470b);

Film-coating: hypromellose 2910 (15 mPa*s) (E464), lactose monohydrate, titanium dioxide (E171), triacetin, iron oxide red (E172).

The product is available in aluminium/aluminium blister (perforated unit dose blisters or non-perforated) or HDPE bottle with a silica gel desiccant and a polypropylene child resistant closure.

2.2.2. Active substance

2.2.2.1. General information

The chemical name of axitinib is N-Methyl-2-[[3-[E-2-pyridin-2-ylethenyl]-1Hindazol-6-yl]sulfanyl]benzamide corresponding to the molecular formula $C_{22}H_{18}N_4OS$. It has a relative molecular mass of 386.47 g/mol and the following structure:

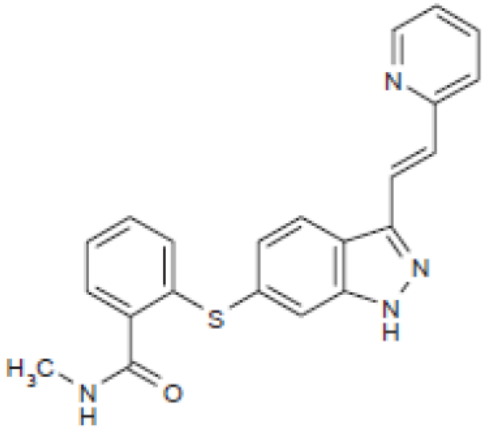


Figure 1: Active substance structure

The chemical structure of axitinib was elucidated by a combination of the following methods: NMR Spectra (Proton ^1H NMR and ^{13}C NMR), Mass Spectrum, FT-IR Spectrum, elemental analysis and XRPD. The solid state properties of the active substance were measured by XRD.

The active substance Axitinib is a white to light yellow hygroscopic powder, soluble in dimethyl sulfoxide, dimethyl formamide and slightly soluble in alcohol. Solubility in different pH buffers is summarised below:

Table 1: solubility of axitinib

Buffer pH	Quantity Dissolved
1.2	10 mg/30 mL
6.0	Insoluble
8.0	Insoluble

Axitinib has no asymmetric carbons, therefore no stereoisomerism is observed.

According to published literature three polymorphic forms of axitinib have been identified: non-solvated axitinib (SAB-I), axitinib monohydrate (SAB-II) and axitinib methanol solvate (SAB-III). Non-solvated axitinib is chosen as the desired form and it was demonstrated that the polymorphic form of the active substance is unchanged during manufacturing and during the shelf life of the finished product.

There is no monograph of axitinib in the European Pharmacopoeia.

2.2.2.2. Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The active substance is obtained from a single source, and it is manufactured at a GMP compliant site.

Axitinib is synthesized in 4 main steps using well defined starting materials (SMs) with acceptable specifications. Following a major objection (MO) raised by the CHMP the proposed SMs have been sufficiently justified in line with ICHQ11 guideline.

During the procedure a major objection was raised on the use of class I solvent in synthesis of one of the starting materials, as this solvent should ideally be avoided. The applicant clarified that the reference to this solvent was an inadvertent error, and it is not used. The major objection was therefore resolved. 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.

The manufacturing process of axitinib was initiated with the thorough literature search. The process developmental activities were initiated and finally optimized for commercial production. Detailed studies were carried out in terms of identification and establishment of quality attributes, optimization of manufacturing scale-up related studies of various laboratory batch scales. Technology of laboratory scale batches were transferred for commercial production.

The active substance is packaged in double transparent polythene bags (LDPE), and HDPE drums. Primary packaging material complies with Commission Regulation (EU) 10/2011, as amended.

2.2.2.3. Specifications

The active substance specifications include tests for appearance, solubility, identity (IR, HPLC, XRPD), water content (KF), sulphated ash, related substances (HPLC), assay (HPLC), residual solvents (GC and HPLC), microbial purity.

The proposed specification was developed and based on development study, results obtained during the validation study, compendial general tests and ICH requirements: ICH Q6A "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances", ICH Q3A "Impurities in New Drug Substances" and ICH Q3C "Impurities: Guideline for Residual Solvents". The specification is suitable to control the pharmaceutical quality of the active substance by the manufacturer and is considered acceptable.

During the procedure, the risk assessment regarding presence of nitrosamine impurities was amended by providing more details around impurities chosen for risk assessment and conclusions regarding limits of detection and quantification of relevant methods. The data provided in response was sufficient to resolve a major objection raised on this issue.

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 testing has been presented.

Batch analysis data on three consecutive commercial scale batches of the active substance are provided. Furthermore, certificates of analysis for three batches of the micronized active substance (manufactured in December 2021, January 2023 and October 2023) are presented. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

Stability data from three, production scale batches of the active substance stored in the intended commercial package for up to 60 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. Moreover, stability data in above conditions are presented for one batch of micronised active substance. This study covers 24 months in long term conditions and 6 months in accelerated conditions.

The following stability indicating parameters were tested during stability study*:* description, identification by IR and XRPD, water content, related substances, assay, microbial purity. All tested parameters are within the specifications.

Results on stress conditions were also provided. Forced degradation study covered high humidity exposed (40°C / 75% RH), thermal degradation (60°C), thermal degradation (solution state, 60°C), photolytic exposed (1.2 million lux hours + UV light 200 watts hrs square meter), oxidative degradation (3% hydrogen peroxide, 24 hours at room temperature), thermal degradation at 105°C, acid degradation (1N hydrochloric acid, 24 hours at room temperature), alkali degradation (1M sodium hydroxide, 6 hours at room temperature). Most degradation was observed in 1M sodium hydroxide.

The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the active substance is stable. The proposed re-test period and storage conditions are: 5 years, preserve in well closed tight light resistant container. Store at or below 25°C are acceptable**.**

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

Axitinib Accord 1 mg film-coated tablets are red coloured, modified capsule shaped biconvex film-coated tablets debossed with 'S14' on one side and plain on other side. The size of the tablet is approximately 9.1 ± 0.2 mm X 4.6 ± 0.2 mm.

Axitinib Accord 3 mg film-coated tablets are red coloured, round, biconvex film-coated-tablet debossed with 'S95' on one side and plain on the other side. The size of the tablet is approximately 5.3 ± 0.3 X 2.6 mm ± 0.3 mm.

Axitinib Accord 5 mg film-coated tablets are red coloured, triangular shaped biconvex film-coated tablets debossed with 'S15' on one side and plain on other side. The size of the tablet is approximately 6.4 ± 0.3 mm X 6.3 ± 0.3 mm.

The finished product has been developed to be a generic equivalent to the reference medicinal product Inlyta. Consequently, the objective was to prepare a dosage form essentially similar to the reference medicinal product. All four strengths were developed i.e. 1, 3, 5 and 7 mg as the reference product, however the 7 mg strength was withdrawn during the procedure as it had not been supported neither by the presented bioequivalence study not by the strength biowaiver data.

The active substance is a BSC class II compound. The active substance attributes that may impact the finished product critical quality attributes were considered empirically by the applicant. Initially, comprehensive information on particle size distribution was not presented, neither was any justification as to and why this potential key parameter is not controlled. In this regard the CHMP requested as a MO, a discussion on the influence of this parameter on the proposed manufacturing process (direct

compression) and homogeneity of active substance in blend and product quality. In order to resolve the major objection, the applicant generated data on the finished product that was evaluated for dissolution with active substance with different particle size from same source having particle size ranging from D (0.9) 24 µm to D (0.9) 44 µm. The study showed no considerable difference in *in-vitro* dissolution profile between studied particle size ranges. Active substance with a larger particle size distribution could not be manufactured complying to the quality attributes of API specification. Thus the applicant was not able to generate dissolution profiles to prove the discriminatory nature of the method by using an active substance with a larger particle size. The overall conclusion that the particle size ranges included in the active substance specifications of the finished product manufacturer are sufficient to assure the performance of the product. This was sufficient to resolve the major objection.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards except ready to use coating material which has in house specification. Ingredients of coating material are of pharmacopoeial quality except iron oxide red. The compliance with Regulation (EU) no 231/2012 has been confirmed. 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 3.1.1 of this report.

Bioequivalence was demonstrated between Axitinib Accord 5 mg film coated tablets and the reference product Inlyta 5 mg film-coated tablets (refer to the clinical part of this report).

Biowaiver of strengths 1 mg and 3 mg has been applied (*in vitro* comparison of dissolution profiles of the 1 mg strength (7U10056A) and 3 mg strength (7V10182B) versus the 5 mg strength (BioBatch 7U10047A) at pHs 1.2, 4.5 and 6.8, in paddle apparatus with 50 rpm, performed on 12 units). The product meets the general requirements according to Guideline on Investigation on Bioequivalence (CHMP/EWP/QWP/1401/98 Rev 01), however the size of batch is below 100 000 tablets. A major objection was raised on the justification regarding the batch size of the 5 mg biobatch and the batch size of the 1 and 3 mg strengths investigated in the in vitro study for the strength biowaiver, and concerns were raised on the dissolution profiles similarity calculations in various media. The applicant confirmed that batch is representative for production/manufacturing process and data generated in response was sufficient to confirm the acceptability of the biowaiver. The applicant has submitted meaningful dissolution profiles and the assessment concludes their similarity.

Axitinib solubility in aqueous media decreases with increasing pH. Aqueous solubility is strongly dependent on pH: it is high in acid (> 2.7 mg/mL at pH 1.2) but low at pH 7.0. The dissolution test conditions (900 mL, 0,01 N HCl, 75 rpm) for routine control.

The discriminatory power of the dissolution method for quality control has been demonstrated. Initially, a major objection was raised on the demonstration of method’s discriminatory power. In response, the applicant has conducted experiments to evaluate the discriminatory power of dissolution method by varying concentrations of excipients used in the formulation to assess formulation variables and also evaluated for different hardness of tablets and different lubrication time tablets to assess process parameters. The provided data and justification of dissolution limits were sufficient to resolve the major objection and assure adequate performance of the product.

The primary packaging is OPA/Aluminium/PVC/Aluminium blisters or HDPE bottles with a silica gel desiccant and a polypropylene child resistant closure, as stated in the SmPC. 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.

2.2.3.2. Manufacture of the product and process controls

During the procedure, lack of GMP compliance was raised as a Major Objection for the finished product manufacturing site. The applicant has then provided satisfactory GMP documentation, which was sufficient to resolve the Major Objection.

The manufacturing process consists of main steps: sifting, blending, lubrication, compression and coating followed by packing. The process is considered to be a non-standard manufacturing process for 1 mg film-coated tablets due to the low amount of active substance in the drug product (≤ 2%) and standard manufacturing process for other doses (the amount of active substance in the drug product is 5%).

Major steps of the manufacturing process have been validated by a number of studies. Validation data of the manufacturing process have been presented for three finished product batches of each strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Lubrication, compression, coating and packaging re considered critical steps of the process. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. Acceptable hold time studies have been performed for two batches of lubricated blend, compressed tablets, coating dispersion and film-coated tablets in bulk.

2.2.3.3. Product specifications

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (HPLC/UV), uniformity of dosage units, average weight, water by KF, dissolution (HPLC), assay (HPLC), related substances (HPLC), and microbial limit test.

The parameters and specification limits of the finished product in the release and shelf-life specifications are in line with ICH requirements and the relevant guidelines.

A description of the tablet in the appearance test is sufficient to identify and discriminate the respective strengths from each other.

The identity of the active substance in the finished product is confirmed in accordance with ICH Q6A, by two methods based on different principles. The average weight is controlled and is considered acceptable. The uniformity of dosage units is demonstrated by content uniformity in line with Ph. Eur. 2.9.40.

The acceptance criteria for assay at release are in line with guideline 3AQ11a. An assay shelf-life specification limit is considered justified regarding the observed levels during storage of the finished product.

A limit for dissolution test is appropriately set. The acceptance criteria for any unspecified impurity at release and shelf-life specifications are in line with ICH Q3B and are acceptable. The limits for Total impurities in the release and shelf-life specifications are set in line with analytical results. The limits for Water content in release and shelf-life specifications are adequate and based on batch analysis and stability data.

Control of microbiological purity is proposed for both specifications in line with Ph. Eur. requirements.

The potential presence of elemental impurities in the finished product has been adequately assessed. Based on the performed evaluation, it is not necessary to include any elemental impurity controls in the finished product specification. A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been adequately performed.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed 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). Additional information was requested , as MO in this respect during the procedure to complement information initially provided. Based on the totality of 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 and the MO was resolved.

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

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three commercial scale batches of each strength of film-coated tablets 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.

2.2.3.4. Stability of the product

Stability data from three commercial scale batches of each strength of the finished product stored for up to 24 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 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 both the primary packaging configurations proposed for marketing.

Samples were tested for description, water content by KF, assay by HPLC, dissolution by HPLC, related substances by HPLC, microbial limit test and water activity. The analytical procedures used are the same as for release and are stability indicating.

No significant changes have been observed.

In addition, a batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results demonstrate that the finished product is not sensitive to light.

Results of in-use stability studies at 25°C ± 2°C / 60% RH ± 5% RH have been presented for batches of all strengths of film-coated tablets packed in HDPE bottle and comply with the acceptance criteria.

Based on presented stability studies results, a shelf-life of 24 months with storage conditions: "This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture" for OPA/Aluminium/PVC/Aluminium blister and "This medicinal product does not require any special temperature storage conditions. Keep the bottle tightly closed to protect from moisture" for HDPE bottle, as stated in SmPC sections 6.3 and 6.4, is considered acceptable for all strengths.

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.

No other excipients derived from animal or human origin have been used.

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. During the procedure there were 7 MOs raised concerning designation of regulatory starting materials, use of solvent in synthesis, nitrosamine risk assessment of the active substance, justification regarding control of active particle size, discriminatory nature of dissolution method, representativeness of the biobatch, and GMP status of the finished product manufacturer. The MOs were all resolved by provision of additional data and justifications 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.

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

Not applicable.

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.

Pharmacodynamic, pharmacokinetic and toxicological properties of axitinib are well known. As axitinib is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

2.3.2. Ecotoxicity/environmental risk assessment

Environmental Risk Assessment was submitted.

In the Phase I assessment, the PECSurfacewater was calculated to be 0.1 µg/L, 0.0001µg/L and 0.0016 µg/L based on default Fpen, Fpen refined based on consumption data and Fpen refined as per epidemiological prevalence data, respectively. The PEC Surfacewater value was below the further action limit of 0.01 µg/L in both the Fpen refined by consumption data and epidemiological data.

2.3.3. Discussion on non-clinical aspects

Based on the Environmental Risk Assessment submitted, Axitinib tablets are unlikely to represent a risk for the environment following its prescribed usage in patients. The non-clinical sections of the SmPC are acceptable.

2.3.4. Conclusion on the non-clinical aspects

Axitinib can be considered approvable from a non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing axitinib. To support the marketing authorisation

application the applicant conducted one bioequivalence study with cross-over design under fasting conditions. The bioequivalence study forms the pivotal basis with an open label, balanced, randomized, two-treatment, two sequence, four-period, single dose, full replicate crossover, 7 days wash-out period BE study.

No formal 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.

Exemption

The bioequivalence study was carried out on Axitinib 5 mg film-coated tablets. Based on acceptable bioequivalence study for Axitinib 5 mg film-coated tablets, a bio-waiver is requested for Axitinib 1 mg, 3 mg film-coated tablets as per following considerations: [*Ref.: CPMP Note for Guidance on Investigation of Bioavailability and Bioequivalence*].

1. Axitinib 1 mg and 3 mg film-coated tablets are manufactured by the same manufacturer and using the same manufacturing process.

2. The composition of Axitinib 3 mg film-coated tablets is dose proportional to BE strength, Axitinib 5 mg film-coated tablets. Axitinib 1 mg film-coated tablet is made as look-a-like formulation to the BE strength 5 mg, where the concentration of excipients are same & the API content is less than 5%.

3. Axitinib plasma pharmacokinetics was dose-proportional, linear pharmacokinetics was observed for the single dose 5 mg to 10 mg dose range. [Ref: CHMP Assessment Report on INLYTA, 24 May 2012, EMA/CHMP/453325/2012]

4. The dissolution profile of Axitinib 1 mg and 3 mg film-coated tablets is similar to Axitinib 5 mg film-coated tablets. The applicant performed in vitro dissolution profiles of the 5 mg strength and the 1 and 3 mg strengths, at pHs 1.2, 4.5 and 6.8, 50 rpm in paddle apparatus.

Since variability was observed at early time points, f_2 calculation was performed with Bootstrapping methodology. Based on the in vitro dissolution profiles between the 5 mg strength and the 1 and 3 mg strengths, at pHs 1.2, 4.5 and 6.8, 50 rpm in paddle apparatus and f_2 with Bootstrapping data the Axitinib 1 mg and 3 mg strengths are meeting the biowaiver criteria described in the guideline on the investigation of bioequivalence.

In vitro comparison of dissolution profiles of the 5 mg strength (BioBatch 7U10047A) and the 1 mg strength (7U10056A) and 3 mg strength (7V10182B), at pHs 1.2, 4.5 and 6.8, 50 rpm in paddle apparatus, performed on12 units, have been submitted as requested.

The applicant provided additional calculations of the expected f2 value for 1mg and 3 mg strengths in 3 media with corrected f2-autoroule selecting 1-profile.

The dissolution profile similarity testing and final conclusions drawn from the results confirm similarity between dissolution profiles of the 5 mg strength and the 1 mg and the 3 mg in three different media pH 1.2; 4,5 and 6,8.

• Tabular overview of clinical studies

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

Table 2: Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study report	Objectives of the study	Study Design & type of control	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	054-21	Refer module 5.3.1.2	**Efficacy** The primary objective was to compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's test product with respect to that of reference product in healthy, adult, human, subjects under fasting conditions and to assess the bioequivalence. **Safety** To monitor the safety and tolerability of the subjects.	An open label, balanced, randomized, two-treatment, two sequence, four-period, single dose, full replicate crossover oral bioequivalence study in healthy, adult, human subjects under fasting conditions.	**Test Product** (T): Axitinib Tablets 5 mg of Shilpa Medicare Limited, India Dose: 1 × 5 mg Batch No.: 7U10047A (Oral) **Reference Product (R)** Inlyta® 5 mg Filmtabletten Axitinib of Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Brussel, Belgien. Dose: 1 × 5mg Lot No.: EL6879 (Oral)	60 healthy adult human subjects participated and 52 subjects completed all four periods of the study.	Normal Healthy Adult Human Subjects	Total duration of the clinical study was 24 days	Completed; Abbreviated

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study 054-21: An open label, balanced, randomized, two-treatment, two sequence, four-period, single dose, full replicate crossover, oral bioequivalence study of Axitinib Tablets 5 mg with Inlyta (Axitinib) 5 mg film-coated tablets of Pfizer Europe MA EEIG, Belgium in healthy, adult, human subjects under fasting conditions.

Study objectives:

- To compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's test product with respect to that of reference product in healthy, adult, human subjects under fasting conditions and to assess the bioequivalence.
- To monitor the safety and tolerability of the product.

Methods

- **Study design**

The study was as an open label, randomized, two-treatment, two sequence, four period, single dose, full replicate crossover, oral bioequivalence study in healthy, adult, human subjects under fasting conditions, with a screening period of 28 days prior to IP administration in period 1. In each study period, 24 blood samples, including one pre-dose blood sample, were collected from each subject to analyse the pharmacokinetic profile of the test as well as the reference product.

Treatment Sequence:

	Period 01	Period 02	Period 03	Period 04
Sequence 1	Treatment-T (Test)	Treatment-R (Reference)	Treatment-T (Test)	Treatment-R (Reference)
Sequence 2	Treatment-R (Reference)	Treatment-T (Test)	Treatment-R (Reference)	Treatment-T (Test)

A washout period of 7 days was considered sufficient between the successive dosing days. The duration of the clinical part of the study was about 24 days (9.0 hours prior to dosing in period 1 until the last pharmacokinetic sample collection in period 4).

After an overnight fasting of at least 8.0 hours, a single oral dose of either test product (Axitinib Tablets 5 mg) or reference product (Inlyta® 5 mg Film tabletten Axitinib) was administered with 240 mL of drinking water at room temperature with the subjects in sitting posture. The IP administration was done as per the randomization schedule and under open-label conditions.

Dose administration was carried out under yellow monochromatic light. The tablets were swallowed whole without chewing or crushing.

A total of 24 blood samples were collected from all the subjects during each period. The blood samples of pre-dose (00.00 hour) of 6 mL and post dose samples of each 04 mL were collected at 0.50, 1.00, 1.50, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.33, 4.67, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 20.00, 24.00 and 36.00 hours post dose.

Safety was assessed from the screening period to the end of the study. It was assessed through clinical examination, vital signs assessment, 12-lead electrocardiogram (ECG), chest X-ray (within the last 6 months) (posterior-anterior view) recording, clinical laboratory parameters [e.g. biochemistry, haematology, urine analysis and immunology].

Urine scan for drugs of abuse and urine alcohol tests were done during check-in of each period.

Vital sign measurement was done at check-in, pre-dose, 2.0, 5.0, 10.0 hours post dose and checkout in each period. The subjects were questioned for well-being and COVID-19 disease symptoms during recording of vital signs in each period.

- **Population(s) studied**

Healthy, adult, human volunteers between 18 to 45 years of age (both inclusive), having a BMI between 18.50 and 30.00 Kg/m2 (both inclusive), were able to understand and comply with the study procedures and having given their written informed consent were checked in for the study. They did not have any significant diseases or clinically significant abnormal laboratory value findings during screening, medical history, clinical examination, laboratory evaluations, 12-lead ECG and chest X-ray (posterior-anterior view) recordings. Urine test for drugs of abuse and urine alcohol test were done during check-in of each period. COVID-19 symptoms assessment was performed during screening, check-in, checkout of each period, post study investigations and ambulatory blood sample collection as per the Safety manual-COVID-19. Volunteers who complied with all the inclusion criteria were checked in for the study.

- **Analytical methods**

A validation process was performed to assess Axitinib in human plasma using LC-MS/MS to support clinical study BE 054-21. The Limit of Quantification was set to 0.201 ng/mL. The detection method was found to be linear at ranges from 0.200 ng/mL to 125.296 ng/mL using 10 point calibration curve (acceptable precision and accuracy). Following parameters were addressed during validation and met the acceptance criteria: selectivity (tested for normal, lipemic and hemolyzed plasma), specificity, precision and accuracy (intra-day-within batch, inter-day-between batch), dilution integrity (1:4), reinjection reproducibility (after storing accepted batch in auto sampler for 1 day and 22 hours).

Stability was approved for following matrices and conditions: stock solution (Room Temperature (RT); 1 day 23 hours; at 5 ± 3ºC; 11 days 22 hours), working solution (RT; 1 day 23 hours; 5 ± 3ºC; 11 days 22 hours and 12 days 20 hours), neat sample (5 ± 3ºC; 11 days 22 hours; at RT; 2 days 3 hours), the bench top stability (1 day 18 hours), wet extract stability (RT; 2 days; 5 ± 3ºC; 2 days 22 hours), five

freeze-thaw cycles stability (-70 ± 15°C; -20 ± 5°C); auto sampler stability (2 days 22 hours to that of comparison samples at autosampler (5°C) temperature), dry-ice stability (1 day 16 hours), solution stability (5 days for mobile phase, mobile phase buffer, diluent solution, rinsing solution and extraction buffer), whole blood stability (Ice-bath; 3 hours 2 minutes; RT; 3 hours 4 minutes).

No matrix effect, measured with 8 different lots (6 normal plasma lots, 1 hemolyzed and 1 lipemic) was detected. No carryover effect was observed. Batch size was determined for 157 samples. No Concomitant Drugs Effect for paracetamol, caffeine, diclofenac, nicotine, ondansetron, pantoprazole, domperidone and cetirizine was detected.

All parameters recommended for analytical method validation were addressed (EMEA/CHMP/EWP/192217/2009) and met the acceptance criteria. Validation seems to be acceptable.

Bioanalysis - Bioanalytical study for the estimation of Axitinib in human K_2EDTA plasma using LCMS/MS to support clinical study BE 054-21 was performed and submitted as report BAL-SR-21-002.

Human plasma samples (5114 samples) were analysed for Axitinib. Before the analysis (BAL-SR-21-002) samples were stored for a maximum time of 84 days.

The applicant provided the results of long-term stability testing, which covered the longest samples storage period of 84 days. The long-term stability study was conducted over 139 days at two temperatures: -70°C ± 15°C and -20°C ± 5°C. The results demonstrated that at both temperature conditions, they fell within the specified range.

Total 66 runs were analysed for Axitinib in human plasma, and 65 met the acceptance criteria. Incurred sample reproducibility was performed for 424 samples; 413 samples (97.41%) of them were acceptable as repeated samples had relative differences not exceeding 20% compared to the first evaluation. Obtained results were within the range of the calibration curve.

- **Pharmacokinetic variables**

Table 3: Primary and Secondary Pharmacokinetic variables

Primary Pharmacokinetic Parameters	
C_{max}	Maximum measured plasma concentration over the time span specified.
AUC_{0-t}	The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.
Secondary Pharmacokinetic Parameters	
AUC_{0-inf}	Area under the plasma concentration versus time curve from time zero to infinity. Where $AUC_{0-inf} = AUC_{0-t} + Ct/\lambda z$, Ct is the last measurable concentration and λz is the terminal rate constant.
T_{max}	Time of the maximum measured plasma concentration.
K_{el}	Apparent first order elimination rate constant calculated from a semi-log plot of plasma concentration versus time point. The parameter will be calculated by linear square regression analysis using the last 3 (or more) non-zero plasma concentrations.
K_{el_lower}	Time point where log-linear elimination begins (h).
K_{el_Upper}	Time at which the last concentration occurred that is above the lower limit of quantitation (h).
$T_{1/2}$	The terminal half-life will be calculated as ln (2)/ K_{el}.
Residual area	The residual area in percentage will be determined by the formula, $[(AUC_{0-inf} - AUC_{0-t})/AUC_{0-inf}] \times 100$.

- **Statistical methods**

For pharmacokinetic parameters

The ln-transformed pharmacokinetic parameters Cmax and AUC0-t were analysed using a PROC GLM effect ANOVA model with the main effect of treatment, period, sequence and subjects nested within sequence as fixed effects

Two one-sided tests were used to test for bioequivalence of each of these parameters.

ANOVA, 90% confidence interval using two one-sided tests for bioequivalence, power and ratio analysis were performed on ln-transformed pharmacokinetic parameters Cmax and AUC0-t for

Axitinib.

The within-subject standard deviation of the reference product (SWR) was calculated for the lntransformed pharmacokinetic parameters Cmax for scaled average bioequivalence. The Intra

subject coefficient of variation was calculated for the ln-transformed pharmacokinetic parameters Cmax and AUC0-t for average bioequivalence.

Criteria for conclusion of bioequivalence are as follows:

Based on the statistical analysis, the test product will be concluded bioequivalent to the reference

product if primary pharmacokinetic parameters Cmax and AUC0-t satisfy below mentioned criterion for Axitinib:

• **For AUC0-t:** 90% confidence intervals for the difference of means of Ln-transformed AUC0-t should fall within 80.00-125.00%.

• **For Cmax:** 90% confidence intervals for the difference of means of Ln-transformed Cmax Should Fall within 80.00-125.00%, if within-subject variability for Cmax of the Reference product in the study is ≤ 30% or Should Fall within widened acceptance range, if within-subject variability for Cmax of the Reference product in the study is > 30% and the geometric mean ratio (GMR) of test to reference for Lntransformed Cmax falls within the acceptance range of 80.00-125.00% or should Fall within widened acceptance range, if within-subject variability for Cmax of the Reference product in the study is > 30% and the geometric mean ratio (GMR) of test to reference for Lntransformed Cmax falls within the acceptance range of 80.00-125.00%

Determination of sample size

Based on the Literature, reported intra subject variability observed for primary pharmacokinetic parameter was found to be ~54%; Hence, considering the CV of 54% the following estimates were considered for the computation of sample size:

T/R ratio = ~ 95.0 to 105.3%

Intra-Subject C.V (%) = ~54%

Significance Level = 5%

Power = 80%

Bioequivalence Limits = 80.00-125.00%

Based on the above estimates, a sample size of 56 subjects were required to establish bioequivalence between formulations with adequate power. However, considering potential withdrawals and dropouts

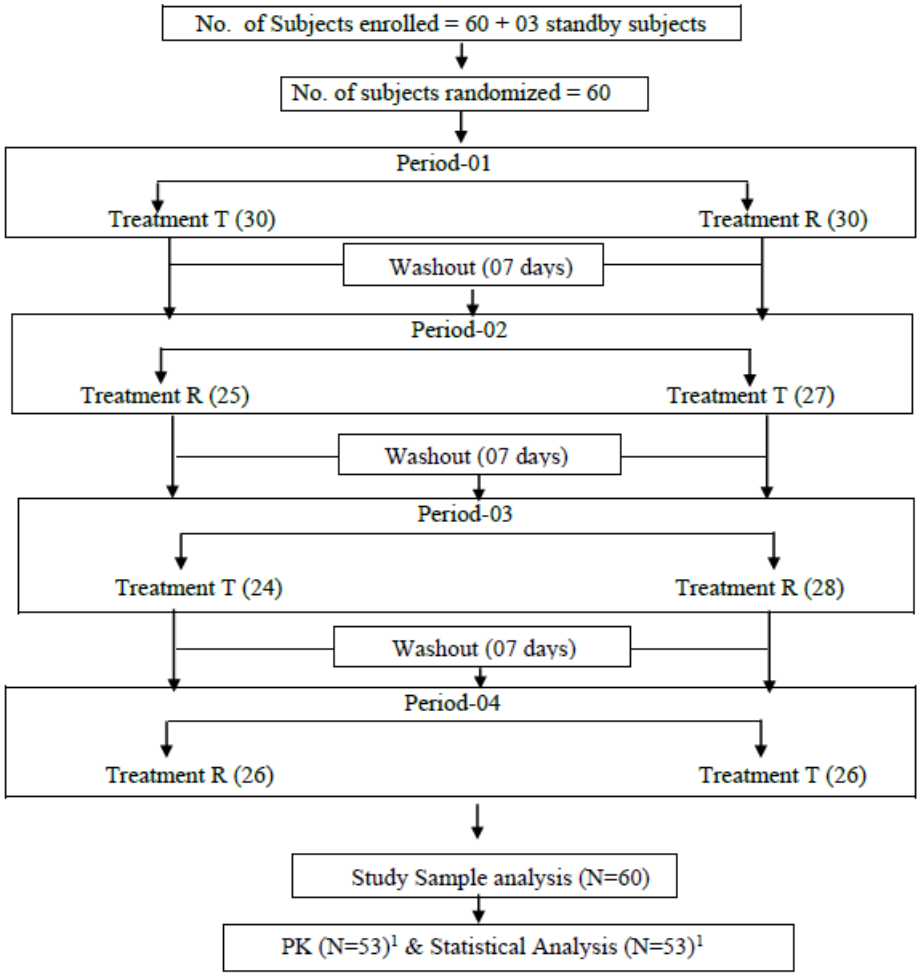
due to adverse events, non-compliance and subject personal reasons etc., 60 subjects were randomized and dosed.

- ***Results***

Disposition of subjects

A total of 63 (60 + 3 standby) subjects were enrolled in the study. A total of 60 subjects have participated in the study. Out of 60, 45 subjects were completed four periods of the study successfully. The 3 standbys who were enrolled to compensate any withdrawal prior to dosing in period 1 were checked out of the facility as none of the subject was discontinued/ withdrawn from the study prior to dosing in period 1.

Flowchart 1. Subject Disposition Flowchart



Total number of subjects who completed Clinical phase of the study: 45
Total number of subjects assayed: 60
Total number of subjects included in pharmacokinetic and statistical analysis: 53

The subject numbers 01, 18, 26, 30, 34, 35 and 43 were excluded pharmacokinetic and statistical analysis, as the subject number 01 was withdrawn from the study due to adverse event (diarrhoea) in period 2 washout, the subject numbers 18 and 34 were withdrawn from the study due to adverse event (vomiting) in period 2, the subject number 26 was withdrawn from the study due to adverse event (vomiting) in period 1, the subject number 30 was withdrawn from the study due to adverse event (epigastric pain) in period 4, the subject number 43 was withdrawn from the study due to

adverse event (diarrhoea) in period 2. For the subject number 35 Reference AUC was less than 5% of overall Reference AUC Geometric mean.

PHARMACOKINETIC EVALUATION

Data Sets Analysed

A total of (60) subjects were participated in the study as per IEC approved protocol. The plasma samples of all 60 subjects were analysed and plasma concentrations of 53 (2-17, 19-25, 27-29, 31-33, 36-42, 44-60) subjects were included in the pharmacokinetic and statistical analysis.

The subject numbers 01, 18, 26, 30, 34, 35 and 43 were excluded pharmacokinetic and statistical analysis, as the subject number 01 was withdrawn from the study due to adverse event (diarrhoea) in period-02 washout, the subject numbers 18 and 34 were withdrawn from the study due to adverse event (vomiting) in period-02, the subject number 26 was withdrawn from the study due to adverse event (vomiting) in period-01, the subject number 30 was withdrawn from the study due to adverse event (epigastric pain) in period-04, the subject number 43 was withdrawn from the study due to adverse event (diarrhoea) in period-02. For the subject number 35 Reference AUC was less than 5% of overall Reference AUC Geometric mean.

Table 4: Summary of Pharmacokinetic Profile of Test Product (T1) for Axitinib

Pharmacokinetic Parameter	N	Arithmetic Mean	Standard Deviation	CV%	Minimum	Median	Maximum	Geometric Mean
C_{max} (ng/mL)	52	40.99	26.312	64.19	3.52	35.78	102.39	31.65
$AUC_{(0-t)}$ (h*ng/mL)	52	178.88	125.613	70.22	10.69	150.20	485.04	129.84
$AUC_{(0-inf)}$ (h*ng/mL)	51	185.73	128.518	69.20	11.02	153.21	488.17	135.86
T_{max} (h)	52	1.89	1.097	58.15	1.00	1.50	4.33	1.64
T_{half} (h)	51	4.58	3.617	78.96	0.67	3.61	17.88	3.62
K_{el} (1/h)	51	0.24	0.192	79.11	0.04	0.19	1.04	0.19
K_{el} Lower (h)	52	6.87	5.645	82.17	1.50	5.50	20.00	4.92
K_{el} Upper (h)	52	22.47	8.716	38.79	4.33	24.00	36.00	20.41
Residual Area (%)	51	2.79	4.296	153.94	0.25	1.08	20.74	1.45
N: Number of Subjects								

Table 5: Summary of Pharmacokinetic Profile of Test Product (T2) for Axitinib

Pharmacokinetic Parameter	N	Arithmetic Mean	Standard Deviation	CV%	Minimum	Median	Maximum	Geometric Mean
C_{max} (ng/mL)	49	36.35	26.526	72.97	4.19	31.10	140.51	27.87
$AUC_{(0-t)}$ (h*ng/mL)	49	162.82	116.621	71.62	4.76	149.04	568.60	120.49
$AUC_{(0-inf)}$ (h*ng/mL)	45	177.23	117.455	66.27	4.99	160.81	570.17	136.92
T_{max} (h)	49	1.96	0.963	49.15	1.00	1.50	4.33	1.75
T_{half} (h)	45	4.71	2.931	62.24	0.45	4.21	16.07	3.81
K_{el} (1/h)	45	0.25	0.290	114.74	0.04	0.16	1.53	0.18
K_{el} Lower (h)	49	5.99	4.751	79.36	1.50	5.00	20.00	4.53
K_{el} Upper (h)	49	23.39	8.570	36.63	3.00	24.00	36.57	21.06
Residual Area (%)	45	2.31	2.333	101.09	0.28	1.66	9.51	1.53
N: Number of Subjects								

Table 6: Summary of Pharmacokinetic Profile of Reference Product (R1) for Axitinib

Pharmacokinetic Parameter	N	Arithmetic Mean	Standard Deviation	CV%	Minimum	Median	Maximum	Geometric Mean
C_{max} (ng/mL)	49	37.54	28.325	75.45	1.52	34.54	152.99	26.50
$AUC_{(0-t)}$ (h*ng/mL)	49	164.10	123.528	75.28	8.22	158.30	513.75	111.55
$AUC_{(0-inf)}$ (h*ng/mL)	45	176.54	123.627	70.03	8.62	163.32	516.55	128.26
T_{max} (h)	49	2.04	1.003	49.10	1.00	2.00	5.50	1.84
T_{half} (h)	45	4.06	2.313	57.00	0.55	3.43	9.60	3.37
K_{el} (1/h)	45	0.27	0.249	93.27	0.07	0.20	1.25	0.21
K_{el} Lower (h)	49	6.49	4.746	73.09	2.00	5.50	20.00	5.26
K_{el} Upper (h)	49	22.29	8.704	39.06	4.67	24.00	35.77	20.08
Residual Area (%)	45	2.46	2.743	111.39	0.20	1.55	12.88	1.53
N: Number of Subjects								

Table 7: Summary of Pharmacokinetic Profile of Reference Product (R2) for Axitinib

Pharmacokinetic Parameter	N	Arithmetic Mean	Standard Deviation	CV%	Minimum	Median	Maximum	Geometric Mean
C_{max} (ng/mL)	52	40.96	31.880	77.84	3.82	31.31	130.89	27.88
$AUC_{(0-t)}$ (h*ng/mL)	52	178.21	138.254	77.58	10.06	158.34	497.88	114.23
$AUC_{(0-inf)}$ (h*ng/mL)	42	200.93	138.547	68.95	10.55	183.63	499.36	139.38
T_{max} (h)	52	1.95	0.858	43.99	1.00	2.00	4.67	1.78
T_{half} (h)	42	5.00	3.140	62.85	0.37	4.66	13.77	3.91
K_{el} (1/h)	42	0.27	0.357	133.07	0.05	0.15	1.87	0.18
K_{el} Lower (h)	52	7.97	5.787	72.63	1.50	5.50	20.00	6.08
K_{el} Upper (h)	52	24.11	8.431	34.96	4.33	24.00	35.30	21.96
Residual Area (%)	42	2.71	3.213	118.37	0.30	1.76	17.26	1.67
N: Number of Subjects								

Figure 2: Mean plasma concentration vs time curve for Axitinib
Linear Plot

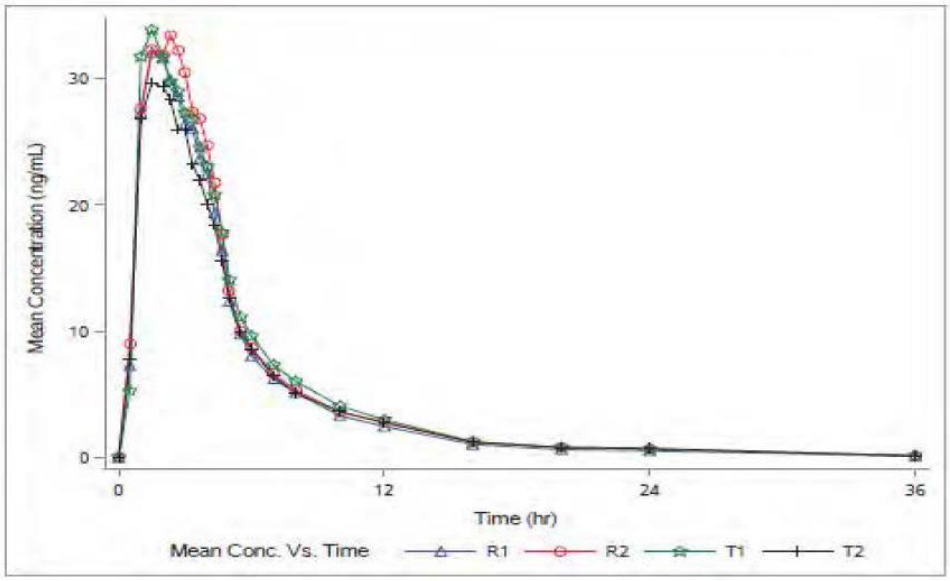
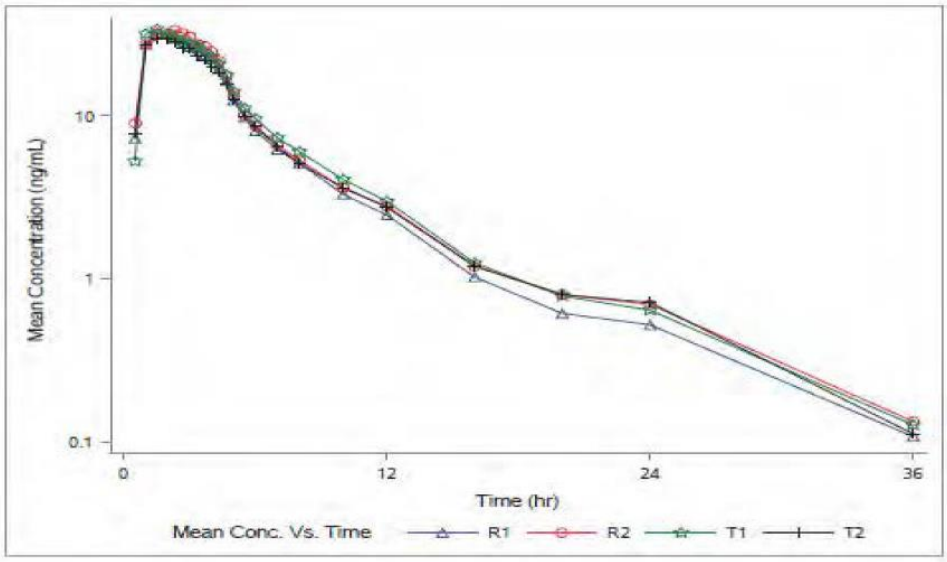


Figure 3: Semi Log Plot



The applicant provided additional statistical calculations including subjects #01 and #30.
The point estimates and 90% confidence intervals for the ln-transformed pharmacokinetic variables C_{max} and AUC $_{0-t}$ were within the predefined bioequivalence range of 69.84% - 143.19 and 80.00% - 125.00%, respectively and therefore the results could indicate bioequivalence between the test and reference products. The within-subject variability for Cmax of the Reference product in the study was > 30%, hence the acceptance limits for Cmax was widened using scaled average bioequivalence.

Statistical Analysis

Statistical analysis on ln-transformed pharmacokinetic parameters Cmax and AUC0-t were performed using PROC GLM of SAS® Version 9.4 (SAS Institute Inc., USA) for Axitinib.

ANOVA p-values for Axitinib are summarized in the following table:

Table 8: ANOVA p-values for axitinib

ANOVA (p-value)			
Parameters	**Formulation**	**Period**	**Sequence**
lnC_{max}	0.3895	0.4070	0.8231
$lnAUC_{0-t}$	0.2891	0.3662	0.8934

Note: p-value is statistically significant if it is < 0.05 for formulation and period effects.
p-value is statistically significant if it is < 0.1 for Sequence effect.

Formulation and Period effects were found to be statistically insignificant for ln-transformed pharmacokinetic parameters Cmax and AUC0-t at 5% level of significance.

Sequence effects was found to be statistically insignificant for ln-transformed pharmacokinetic parameters Cmax and AUC0-t at 10% level of significance.

- **Safety data**

Subject Exposure: A total of 63 (60 + 03 standby) subjects were checked-in for the study. Sixty (60) subjects were dosed in period-01. The safety assessment includes information for all 60 subjects who were dosed during the study.

Table 9: Subject exposure

Period	01	02	03	04
Number of subjects received Test Product-T	30	27	24	26
Number of subjects received Reference Product-R	30	25	28	26
Exposure	1 × 5 mg	1 × 5 mg	1 × 5 mg	1 × 5 mg

Adverse events

The clinical portion of the study was completed with twenty-one AEs in fifteen subjects (subject numbers 01, 07, 14, 15, 18, 23, 26, 27, 30, 34, 36, 43, 47, 50 and 60).

The reported AEs were T-inversions in V1-V2, Nausea, Vomiting, T-inversions in V1-V4, T-inversions in lead II, III, avF, T-wave inversions in leads V1-V5, T-wave inversions in V1-V6, Sinus tachycardia, T-wave inversions in V2-V6, Diarrhoea, Itching (Pruritus), T inversions in II, III, avF, T-wave inversions and Epigastric pain (Abdominal pain upper).

Out of the twenty-one AEs, nine AEs were occurred following administration of the test product and twelve AEs were occurred following administration of the reference product.

The AEs occurred with administration of test product and reference products were possible related.

All adverse events were mild to moderate in intensity. All the adverse events were resolved.

No deaths or serious adverse events were reported during the conduct of the study.

Overall the study, Axitinib Tablets 5 mg was well tolerated as a single oral dose when administered under fasting conditions.

2.4.2.2. Pharmacodynamics

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

2.4.2.3. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.3. Discussion on clinical aspects

The applicant conducted one bioequivalence study under fasting conditions to demonstrate that the Test Product – Axitinib Accord, 5mg film-coated tablets is bioequivalent to the Reference Product – INLYTA, 5mg film-coated tablets.

Generally, the design of the performed BE study (open label, balanced, randomized, two-treatment, two sequence, four-period, single dose, full replicate crossover, 7 days wash-out period) is considered acceptable. Choice sampling points, overall sampling time as well as wash-out period were adequate.

However, it should be noted that the reference product Inlyta is approved at the higher strength of 7 mg.

During the assessment, the 7 mg strength was not considered approvable as in line with the Guideline on the investigation of bioequivalence for drugs with linear PK, the bioequivalence study should in general be conducted at the highest strength. For products with linear pharmacokinetics and where the drug substance is highly soluble, selection of a lower strength than the highest is also acceptable. Selection of a lower strength may also be justified if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons. For low solubility drugs, the highest strength is the most sensitive to detect differences between formulations or products. A lower strength can be tested only if there are safety problems that preclude the use of healthy volunteers. Therefore, the 7 mg strength of Axitinib Accord is not considered approvable and the applicant decided to withdraw this strength during the procedure.

The analytical method was validated. Pharmacokinetic and statistical methods applied are adequate.

The point estimates and 90% confidence intervals for the ln-transformed pharmacokinetic variables C_{max} and AUC $_{0-t}$ were within the predefined bioequivalence range of 69.84% - 143.19 and 80.00% - 125.00%, respectively and therefore the results could indicate bioequivalence between the test and reference products. The within-subject variability for Cmax of the Reference product in the study was > 30%, hence the acceptance limits for Cmax was widened using scaled average bioequivalence.

No new emerging safety issues were reported during the studies. No serious adverse events were reported.

Based on the presented bioequivalence study No 054-21 Axitinib 5mg film-coated tablets can be considered bioequivalent with INLYTA 5mg film-coated tablets.

Following further requests, the applicant provided the expected f2 value calculations for 3 mg strengths in media pH 1.2 and 6,8 and the updated f2 calculations (for all strengths at all pHs) correcting the f2-autorule and selecting 1-profile.Based on the presented results of the dissolution comparison, it can be concluded that in-vitro dissolution profiles of test product and reference product for 1mg, 3mg and 5 mg strengths are comparable.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence study No.054-21, Axitinib Accord 5mg film-coated tablets is considered bioequivalent with INLYTA, 5mg film-coated tablets.

The results of study No.054-21 with 5 mg formulation can be extrapolated to other strengths 1mg and 3mg according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

A summary of the literature with regard to clinical data of axitinib was provided and is accepted by the CHMP.

2.5. Risk Management Plan

2.5.1. Safety concerns

2.5.1.1. Summary of safety concerns

Safety Specification

The Safety Specification (Part II, SVIII) from RMP version 1.0, dated 27-10-2022 is presented below:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Arterial embolic and thrombotic events Gastrointestinal perforation and fistula Haemorrhage Posterior Reversible Encephalopathy Syndrome Venous Embolic and Thrombotic Event Effects on the exocrine pancreas Renal failure Congestive heart failure/cardiomyopathy
Important potential risks	Torsade de pointes due to QT prolongation Reproductive and developmental toxicity Carcinogenicity Osteonecrosis of the jaw
Missing information	Risks in pregnant and lactating women Risks in paediatric subjects Risks in subjects with moderate and severe renal impairment (serum creatinine >1.5 times the ULN (Upper Limit of Normal) or calculated creatinine clearance <60 mL/min) Risks in subjects with severe hepatic impairment (Child-Pugh Class C) Risks in subjects with brain metastasis, spinal cord compression, or carcinomatous meningitis Risks in subjects with active peptic ulcer disease Risks in subjects with a recent major surgery (within 4 weeks) or radiation therapy (within 2 weeks)

2.5.2. Discussion on safety specification

Having considered the data in the safety specification, the safety concerns listed by the applicant are considered appropriate.

2.5.3. Conclusions on the safety specification

Having considered the data in the safety specification, it is agreed that the safety concerns listed by the applicant are considered appropriate.

2.5.4. Pharmacovigilance plan

No additional pharmacovigilance activities have been proposed, in line with the RMP of the reference product.

2.5.5. Risk minimisation measures

No additional risk minimisation measures have been proposed, in line with the RMP of the reference product.

2.5.6. Conclusion

The CHMP and PRAC considered that the Risk management plan version 1.0, dated 27-10-2022 is acceptable. No new risks have been identified for the generic product that are not recognised for the reference product and there are no outstanding issues.

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

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 Inlyta. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of axitinib, 5mg, film-coated tablets. The reference product Inlyta is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical 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 is considered sufficient.

The bioequivalence study forms the pivotal basis with an open label, balanced, randomized, two-treatment, two sequence, four-period, single dose, full replicate crossover, 7 days wash-out period BE study. The study design is 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 are adequate.

The test formulation of Axitinib, 5mg, film-coated tablets met the protocol-defined criteria for bioequivalence when compared with the Inlyta, 5mg, film-coated tablets.

The point estimates and 90% confidence intervals for the ln-transformed pharmacokinetic variables C_{max} and AUC $_{0-t}$ were within the predefined bioequivalence range of 69.84% - 143.19 and 80.00% - 125.00%, respectively and therefore the results could indicate bioequivalence between the test and reference products. The within-subject variability for Cmax of the Reference product in the study was > 30%, hence the acceptance limits for Cmax was widened using scaled average bioequivalence.

Based on the presented results it is concluded that *in-vitro* dissolution profiles of test product and reference product for all strengths are comparable**.**

However, it should be noted that the reference product Inlyta is approved at the higher strength of 7 mg.

During the assessment, the 7 mg strength was not considered approvable as in line with the Guideline on the investigation of bioequivalence for drugs with linear PK, the bioequivalence study should in general be conducted at the highest strength. For products with linear pharmacokinetics and where the drug substance is highly soluble, selection of a lower strength than the highest is also acceptable. Selection of a lower strength may also be justified if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons. For low solubility drugs, the highest strength is the most sensitive to detect differences between formulations or products. A lower strength can be tested only if there are safety problems that preclude the use of healthy volunteers. Therefore, the 7 mg strength of Axitinib Accord is not considered approvable and the applicant decided to withdraw this strength during the procedure.

Based on the presented results it can be concluded that *in-vitro* dissolution profiles of test product and reference product for both strengths of 1mg and 3 mg are comparable and Axitinib Accord 1mg, 3mg and 5mg film-coated tablets is considered bioequivalent to Inlyta, 1mg, 3mg and 5mg film-coated tablets.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Axitinib Accord 1 mg, 3 mg and 5 mg film-coated tablets is favourable in the following indication:

Treatment of adult patients with advanced renal cell carcinoma (RCC) after failure of prior treatment with sunitinib or a cytokine.

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.