10 December 2020
EMA/CHMP/2430/2021
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Sunitinib Accord

International non-proprietary name: sunitinib

Procedure No. EMEA/H/C/005419/0000

## 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
AEs Adverse events
AML Acute myelogenous leukaemia
AP Applicant's Part (or Open Part) of a DMF
API Active Pharmaceutical Ingredient
AR Assessment Report
ASM Active Substance Manufacturer
ASMF Active Substance Master File = Drug Master File
AUC Area under the plasma concentration–time curve
AUC0-24 Area under the plasma concentration–time curve from zero to 24 h
AUC0 – ∞ Area under the plasma concentration – time curve to infinity
AUC0-t Area under the plasma concentration-time curve from zero to the time of last measurable concentration
BICR Blinded independent central review
BOR Best overall response
CBR Clinical benefit rate
CDD Continuous daily dosing
CEP Certificate of Suitability of the EP
CFU Colony Forming Units
CI Confidence interval
CIDP Chronic inflammatory demyelinating polyneuropathy
CL/F Fractional oral systemic clearance
Cmax Maximum observed peak plasma concentration
CMS Concerned Member State
CoA Certificate of Analysis
COSY Correlation spectroscopy
CRS Chemical Reference Substance (official standard)
CSF-1R colony stimulating factor receptor Type 1
CYP3A4 Cytochrome P450-3A4
DEPT Distortionless Enhancement by Polarization Transfer
DMF (1) Drug Master File = Active Substance Master File, (2) Dimethylformamide
DP Decentralised (Application) Procedure
DR Duration of response
DSC Differential Scanning Calorimetry
ECOG Eastern Cooperative Oncology Group
EDQM European Directorate for the Quality of Medicines
ESRD End-stage renal disease
FACT-G Functional Assessment of Cancer Therapy - General
FDA Food and Drug Administration
FFS Failure-free survival
FGFR1 Fibroblast growth factor receptor 1
FKSI FACT Kidney Symptom Index
FLT3 Fms-like tyrosine kinase-3
GC Gas Chromatography
GEP-NETs Gastroenteropancreatic neuroendocrine tumours
GI Gastrointestinal
GIST Gastrointestinal stromal tumour

GSM Grams per square meter
hERG Ether-à-go-go-Related Gene
HIF1-a Hypoxia-inducible factor 1-a
HMBC Heteronuclear Multiple Bond Correlation
HMQC Heteronuclear Multiple Quantum Coherence
HPLC High Performance Liquid Chromatography
HR Hazard ratio
HRQoL Health-related quality of life
IC50 Half-maximal Inhibitory concentration
IDS Initial dosing schedule
IFN-α Interferon alpha
IL Interleukin
IPC In-process control
IR Infrared
ITD Internal tandem duplication
ITT Intention to treat
IU International Units
KF Karl Fischer
KIT Stem cell factor receptor
LDPE Low Density Polyethylene
LOA Letter of Access
LOD Limit of Detection
LOQ (1) Limit of Quantification, (2) List of Questions
MA Marketing Authorisation
MAH Marketing Authorisation Holder
MEB Medicines Evaluation Board
MS Mass Spectrometry
ND Not detected
NETs Neuroendocrine tumours
NLT Not less than
NMR Nuclear Magnetic Resonance
NMT Not more than
NST Neoadjuvant sunitinib therapy
NT Not tested
ONJ Osteonecrosis of the jaw
OOS Out of Specifications
ORR Objective response rate
OS Overall survival
p.o. Per os, orally
PDE Permitted Daily Exposure
PDGFR Platelet-derived growth factor receptor
PE Polyethylene
PFS Progression-free survival
Ph.Eur. European Pharmacopoeia
PIL Patient Information Leaflet
PNENs Pancreatic neuroendocrine neoplasms
pNET Pancreatic neuroendocrine tumour
pNETs Pancreatic neuroendocrine tumours

PRs Partial responses
QOL Quality of Life
QOS Quality Overall Summary
RCC Renal cell carcinoma
RET Glial cell-line derived neurotrophic factor receptor
RH Relative Humidity
RP Restricted Part (or Closed Part) of a DMF
RPSFT Rank-preserving structural failure time
RRT Relative retention time
RSD Relative standard deviation
RTKs Receptor tyrosine kinases
RVG # Marketing Authorisation number in NL
SD Stable disease
SDF Stromal cell-derived factor
sKIT Soluble KIT
SLF Steel factor
SPC Summary of Product Characteristics
sVEGFR-2 Soluble VEGFR-2
sVEGFR-3 Soluble VEGFR-3
t1/2 Half-life
TD Total drug
TGA Thermo-Gravimetric Analysis
TLC Thin Layer Chromatography
TMA Thrombotic microangiopathy
Tmax Time to reach maximum plasma concentration
UV Ultraviolet
Vd Volumes of distribution
Vd/F Volume of distribution
VEGFR Vascular endothelial growth factor receptor
VHL von Hippel–Lindau
Vss Volume of distribution at steady-state
WT Wild-type
XRD X-Ray Diffraction

* 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 14 October 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Sunitinib 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 25 July 2019.

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

The applicant applied for the following indication:

Sunitinib Accord is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after failure of imatinib treatment due to resistance or intolerance.

Sunitinib Accord is indicated for the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults.

Sunitinib Accord is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults.

**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 Sutent 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: Sutent hard capsules, 12.5mg, 25mg, 37.5mg, 50mg
- Marketing authorisation holder: Pfizer Europe
- Date of authorisation: 19-07-2006
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/06/347/001-008

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: Sutent, 50 mg, hard capsules
- Marketing authorisation holder: Pfizer Europe
- Date of authorisation: 19-07-2006
- Marketing authorisation granted by:

  - Union
  - Marketing authorisation number(s): EU/1/06/347/003, EU/1/06/347/006
- Bioavailability study number(s): 17-VIN-0703

## *Information on paediatric requirements*

Not applicable

## *Information relating to orphan market exclusivity*

## Similarity

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

### *Scientific advice*

The applicant did not seek Scientific advice from the CHMP.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Tomas Radimersky Co-Rapporteur: N/A

| | |
|---|---|
| The application was received by the EMA on | 14 October 2019 |
| The procedure started on | 31 October 2019 |
| The Rapporteur's first Assessment Report was circulated to all CHMP members on | 20 January 2020 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on | 31 January 2020 |
| The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on | 27 February 2020 |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 14 August 2020 |
| The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on | 21 September 2020 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 1 October 2020 |
| The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on | 15 October 2020 |

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|---|---|
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 10 November 2020 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on | 25 November 2020 |
| 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 Sunitinib Accord on | 10 December 2020 |
| The CHMP adopted a report on similarity of Sunitinib Accord with SomaKit, Lutathera and AYVAKYT on (Appendix 1) | 10 December 2020 |

# 2. Scientific discussion

## *2.1. Introduction*

## *2.2. Quality aspects*

### 2.2.1. Introduction

The finished product is presented as hard capsules containing 12.5, 25, 37.5 or 50 mg of sunitinib.

Other ingredients are:

Sunitinib Accord 12.5 mg hard capsules

*Capsule content:* cellulose microcrystalline, mannitol (E421), croscarmellose sodium, povidone (E1201) and magnesium stearate.

*Capsule shell*: gelatin, titanium dioxide (E171), red iron oxide (E172) and printing ink white.

*Printing ink white*: shellac, titanium dioxide (E171) and propylene glycol.

Sunitinib Accord 25 mg hard capsules

*Capsule content:* cellulose microcrystalline, mannitol (E421), croscarmellose sodium, povidone (E1201) and magnesium stearate.

*Capsule shell*: gelatin, titanium dioxide (E171), black iron oxide (E172), red iron oxide (E172), yellow iron oxide (E172) and printing ink white.

*Printing ink white*: shellac, titanium dioxide (E171) and propylene glycol.

Sunitinib Accord 37.5 mg hard capsules

*Capsule content:* cellulose microcrystalline, mannitol (E421), croscarmellose sodium, povidone (E1201) and magnesium stearate.

*Capsule shell*: gelatin, titanium dioxide (E171), yellow iron oxide (E172) and printing ink black.

*Printing ink black*: shellac, black iron oxide (E172), propylene glycol and ammonium hydroxide.

Sunitinib Accord 50 mg hard capsules

*Capsule content:* cellulose microcrystalline, mannitol (E421), croscarmellose sodium, povidone (E1201) and magnesium stearate.

*Capsule shell*: gelatin, titanium dioxide (E171), black iron oxide (E172), red iron oxide (E172), yellow iron oxide (E172) and printing ink white.

*Printing ink white*: shellac, titanium dioxide (E171) and propylene glycol.

The product is available in white aluminium-OPA/Alu/PVC blisters, aluminium-OPA/Alu/PVC perforated unit dose blisters and high-density polyethylene (HDPE) bottles with child resistant polypropylene closures as described in section 6.5 of the SmPC.

## 2.2.2. Active substance

***General information***

The chemical name of sunitinib is *N*-(2-(diethylamino)ethyl)-5-((Z)-(5-fluoro-1,2-dihydro-2-oxo-3*H*-indol-3-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxamide corresponding to the molecular formula $C_{22}H_{27}FN_4O_2$. It has a relative molecular mass of 398.47 g/mol and the following structure in Figure 1:

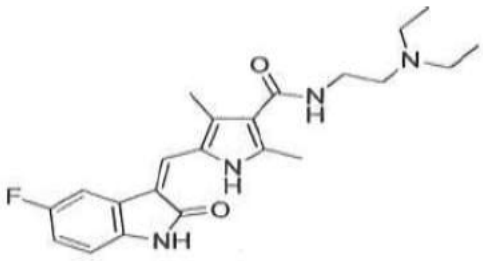


**Figure 1: active substance structure**

The chemical structure of sunitinib was inferred from the route of synthesis and elucidated by a combination of Infra-red spectroscopy (IR), Nuclear Magnetic Resonance spectroscopy (NMR) (1H-NMR and 13C-NMR) and Mass spectrometry.

The active substance is a yellow or orange yellow non-hygroscopic powder which has low pH-dependent solubility in aqueous media. It is more soluble in strongly acidic media but practically insoluble above pH 5.

Sunitinib exhibits polymorphism. The polymorphic forms of Sunitinib can be distinguished by XRD and the manufacturing process followed and described in the ASMF is capable of consistently producing same polymorphic form of Sunitinib.

Sunitinib is achiral.

***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.

Three sites are involved in the manufacture of the active substance; one site performs the manufacture of one intermediate, the second one performs the manufacture of another intermediate and the third one performs the manufacture of the final AS. The starting materials are introduced in

the defined manufacturing process. The starting materials are acceptable and are controlled by suitable specifications. In addition, acceptable specifications for reagents, solvents and other materials used in the synthesis have been provided. Critical steps of the process were identified and are controlled by justified and appropriate in-process controls.

The characterisation of the active substance and its impurities is 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 information presented regarding potential impurities/degradation products controlled in the active substance is sufficient. Overall, the defined control strategy is satisfactory.

Sunitinib is packed in a white LDPE bag within a black polyethylene bag, stored within a triple laminated aluminium foil bag inside a fibre drum with silica gel desiccant, the combination of which provides moisture and light protection. The bags are filled with argon. The primary packing material complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

***Specification***

The active substance specification includes tests for appearance, identification (IR, XRD), water content (KF), sulfated ash (Ph. Eur.), related substances (HPLC), assay (potentiometry), residual solvents (GC), particle size distribution (Ph. Eur.), and microbiological examination (Ph. Eur.).

The specification limits for impurities/degradation products and residual solvents, are in accordance with the requirements of ICH guidelines Q3A and Q3C. All solvents used throughout the entire synthetic process, including those employed prior to the starting material, are routinely controlled in the specification and specified at levels below the ICH Q3C thresholds.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. The finished product manufacturers have adopted the analytical methods for appearance, related substances, assay and residual solvents from ASMF holder. All other analytical methods are Ph. Eur. The specification of the finished product manufacturer is fully in line with the specification of the active substance manufacturer. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data from several production scale batches generated by both active substance and finished product manufacturers is provided, demonstrating compliance with the proposed specifications. The batch data provided is considered to be sufficient. Consistency and uniformity of the active substance quality have been demonstrated.

***Stability***

Stability data from several commercial scale batches of active substance from the proposed manufacturer stored for up to 12 months under long term conditions (5±3°C) and for up to six months under accelerated conditions (25±2°C/ 65±5% RH) according to the ICH guidelines were provided. Some of these batches were manufactured using intermediate from a previous manufacturer. The accelerated study in the current container from long term batch and several accelerated batches were stored in the intended commercial pack, (argon-purged white LDPE bags inside argon-filled black polyethylene bags inside argon-filled triple laminated aluminium bags inside fibre drums with silica gel desiccant) and the other batches were stored in the previous packaging format.

All tested parameters were within the specifications. In the original pack stored at 25°C / 60% RH, an upwards trend for impurities was observed. Therefore, a more protective format was introduced and the favoured storage conditions changed from 25°C / 60% RH to 5 ± 3°C.

Forced degradation studies were conducted for related substances under different stressed conditions like acid, alkali, hydrogen peroxide and thermal. The related substances method was shown to be stability indicating. The peak purity of sunitinib and degradation product peaks under all stressed conditions, was satisfactory.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 42 months stored in the proposed revised packaging, protected from light and at a temperature between 2 and 8°C.

## 2.2.3. Finished medicinal product

***Description of the product and Pharmaceutical development***

The drug product is a hard capsule for oral administration containing 12.5, 25, 37.5 and 50 mg of sunitinib. The capsules presented as follows:

12.5 mg: Gelatin capsules of size 4 with orange cap and orange body, printed with white ink "12.5 mg" on the body and containing yellow to orange granules.

25 mg: Gelatin capsules of size 3 with caramel cap and orange body, printed with white ink "25 mg" on the body and containing yellow to orange granules.

37.5 mg: Gelatin capsules of size 2 with yellow cap and yellow body, printed with black ink "37.5 mg" on the body and containing yellow to orange granules.

50 mg: Gelatin capsules of size 1 with caramel cap and caramel body, printed with white ink "50 mg" on the body and containing yellow to orange granules.

Sunitinib 12.5, 25, 37.5 and 50 mg hard capsules were developed to be physically and chemically stable for the assigned shelf life and equivalent to the reference product Sutent hard capsules, with microcrystalline cellulose as the only difference in the qualitative composition. In addition, Sunitinib Accord uses the free base of the active substance whereas the reference product is manufactured with the malate salt.

Sunitinib is practically insoluble in water, very slightly soluble in methanol and alcohol, slightly soluble in dichloromethane and sparingly soluble in *N*,*N*-dimethylformamide. It also exhibits a pH dependent solubility gradient with the highest solubility observed in acidic media. Sunitinib is a BCS class IV compound with low solubility and low permeability across physiological pH range.

A compatibility study was performed to examine the interaction between the active substance and the proposed excipients. Binary mixtures of sunitinib and each excipient as well as the final formulation mixture were wetted with water in a pre-defined ratio, dried and then stressed for 4 weeks at 40°C/75% RH in open amber glass vials. The HPLC test results for impurity levels indicated no or only small increase in impurities. No incompatibility has been found.

The whole formulation development was conducted on the highest strength capsule and then designed proportionally to create the lower, 12.5, 25, and 37.5 mg strengths. The formulation development of the 50 mg capsule is presented. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The stability of representative formulation batches stored for a period of 6 months under accelerated conditions was satisfactory and as such the final formulation and process were established.

Based on clinical and pharmacokinetic characteristics (PK) as well as the *in vitro* dissolution and physicochemical characteristics of the reference product a quality target product profile was defined.

The main critical quality attributes were defined. These are identified as attributes that may be impacted by formulation and/or process variables and were therefore investigated formulation and process development studies.

The formulation used during clinical studies is the same as that intended for marketing.

Essential similarity between the reference product and the proposed product has been shown through pharmaceutical equivalence testing and two pivotal bioequivalence studies (fasted and fed conditions) between the 50 mg strengths of the test and reference product. Comparative dissolution, assay and impurity profiles of sunitinib 50 mg hard capsules and the innovator product as used in the BE studies have been presented.

However, the test product is considered to be bioequivalent to the reference product based on the clinical bioequivalence studies.

The comparison of the dissolution profile in 0.1 N HCL of the bio-batch and other five 50 mg strength pilot batches of Sunitinib 50 mg hard capsules proved that the bio-batch is representative of the other batches manufactured using the intended commercial process.

Additionally, the applicant requested a biowaiver of lower strengths 12.5 mg, 25 mg and 35.7 mg on the basis that the conditions defined in the Guideline on the investigation of bioequivalence were fulfilled: all the strengths are manufactured by the same manufacturer and by the same manufacturing process, the qualitative composition of all strengths is the same, and the proposed formulations of the 12.5 mg, 25 mg, 37.5 mg and 50 mg (bio strength) capsules are dose proportional.

The individual dissolution results, average and RSD values have been provided. Similarity factors were calculated where applicable (pH 4.5 and 6.8). The results of the *in vitro* dissolution study indicate that the dissolution profiles of Sunitinib 12.5, 25 and 37.5 mg are similar to the bio-batch of Sunitinib 50 mg.

Because of the different salt form in the reference product, solubility of sunitinib base and sunitinib malate were measured in different media in pH range. Based on this, it is concluded that the solubility of sunitinib base is highly pH dependent.

The ability to discriminate between compliant and non-compliant batches was tested by comparison of a batch with proposed qualitative and quantitative composition and a batch with a different amount of binder and diluent. The dissolution profiles in the current proposed QC medium showed a much lower dissolution rate in the non-compliant batch. The discriminatory power of the dissolution method has been demonstrated satisfactorily.

The primary packaging is white aluminium-OPA/Alu/PVC blisters, aluminium-OPA/Alu/PVC perforated unit dose blisters and high-density polyethylene (HDPE) bottles with child resistant polypropylene closures. The materials comply with Ph. Eur. and EC requirements. The choice of container closure systems has been validated by stability data and is adequate for the intended use of the product.

***Manufacture of the product and process controls***

The finished product is manufactured by two manufacturers. The manufacturing process consists of 5 main steps: dispensing (weighing and sieving), granulation, drying, blending and filling. The process is considered to be a standard manufacturing process.

The same manufacturing process is at both of the proposed commercial manufacturing sites.

The critical steps identified are drying of the granules, capsule filling and packaging controlled by several IPCs. 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. The proposed holding times are acceptable. The manufacturing process has been described in sufficient detail and the in-process controls are adequate for hard capsules.

Process validation data on several commercial scale batches at the respective batch sizes were provided. All batches met the in-process and finished product acceptance criteria. The presented process validation data confirm that the process is adequately controlled.

***Product specification***

The finished product release and shelf life specifications include appropriate tests and limits for description (visual), identification of sunitinib (HPLC, UV), identification of titanium dioxide (in house), identification of iron oxide (in house), assay (HPLC), related substances (HPLC), dissolution (HPLC), uniformity of dosage units (Ph.Eur. content uniformity), water content (KF), uniformity of mass (Ph. Eur.) and microbial examination (Ph. Eur.).

The potential presence of class 1 and 2A elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities by both finished product manufacturers. No Type 2B or Type 3 elemental impurities were included because none of them are intentionally added during manufacture of the raw materials. Batch analysis data on several batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

Risk assessments, in line with the "Questions and answers on Information on nitrosamines for marketing authorisation holders" and the "Information on nitrosamines for marketing authorisation holders" published on the EMA website, have been presented for the finished product manufacturing process for both manufacturers and the active substance with respect to potential formation of nitrosamine impurities. The risk of nitrosamine contamination due to the API has been discussed in the risk assessment of the API supplier who provided the confirmatory testing of three batches by a validated GC-MS method and no nitrosamine was detected.

A further risk of nitrosamine formation comes from the presence of the tertiary amine moiety in the API which could potentially react with any nitrite impurities present in the excipients or packaging during finished product manufacture. Sunitinib is indicated for the treatment of advanced cancer and as such, limits for nitrosamines in the finished product would be set in line with ICH Q3B. The MAA commits to submitting a consolidated risk evaluation further considering all of the above aspects by end of March 2021 and to conducting confirmatory testing of API and finished product by end of 2021. This is considered acceptable given the posology and advanced cancer indication. The benefit/risk of the product is considered positive despite this outstanding issue which will be addressed post-approval.

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

Batch analysis data was provided for several full-scale batches per presentation of 25 mg and 37.5 mg and several full-scale batches per presentation of 12.5 mg and 50 mg manufactured at one finished product manufacturing site; and several full-scale batches per presentation manufactured at the other

finished product manufacturing site, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

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

***Stability of the product***

Stability data from several production scale batches of 12.5 and 50 mg capsules and several production scale batches of 25 and 37.5 mg capsules were manufactured and were tested for their stability. Several validation batches were manufactured at one of the finished product manufacturers and other several validation and pilot scale stability batches were manufactured at the second finished product manufacturer. Batches were stored for up to 36 months under long term conditions (25ºC ± 2ºC / 60% ± 5% RH), up to 12 months under intermediate conditions (30°C ± 2°C, 65% ± 5% RH) and for up to 6 months under accelerated conditions (40°C ± 2°C, 75% ± 5% RH) according to the ICH guidelines. The batches of Sunitinib Accord hard capsules are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. The tested batches were packed either in aluminium-OPA/Alu/PVC blisters, HDPE bottles with PP child resistant closure or in the bulk packaging.

The analytical procedures used are stability indicating. No significant changes have been observed and the same manufacturing process is applied at both sites.

In addition, Sunitinib finished product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products, packaged in both blisters and HDPE bottles. The results of the study indicate that upon direct exposure, the product is not sensitive to light, so for Sunitinib 12.5, 25, 37.5 and 50 mg hard capsules in aluminium-OPA/Alu/PVC blisters and in HDPE bottles, no special storage conditions with respect to light are required.

A forced degradation study was also carried out. The results obtained confirm the stability indicative nature of the assay and related substances methods under thermal, alkaline, acidic and aqueous hydrolysis conditions. The active substance degrades significantly under oxidative conditions.

According to the obtained stability results under accelerated and long-term conditions packed in HDPE bottles and additional open-dish studies, there is no indication that Sunitinib hard capsules are susceptible to deterioration and therefore no in-use stability studies have been performed. Usually, the storage condition "Store in the original packaging to protect from moisture" is applied to gelatin capsules, which are known to be sensitive to moisture. The open dish study has proved that the water content only increases slightly, and that appearance, assay, dissolution, and related substances are not affected after one-month storage at 25°C/60% RH. Therefore, the statement regarding protection from moisture is not required.

Based on available stability data, the proposed shelf-life of 36 months with no special storage conditions as stated in the SmPC (section 6.3) is acceptable.

***Adventitious agents***

Gelatine obtained from bovine sources is used in the product. Valid TSE CEPs from the suppliers of the gelatine used in the manufacture are provided.

## 2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and

uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. Sunitinib Accord capsules of all strengths have been shown to be bioequivalent to the reference product. However, the MAA submitted a partial risk assessment concerning the presence of nitrosamine impurities in the medicinal product. The result of confirmatory testing provided by API supplier is that no nitrosamine was detected. Sunitinib is indicated for the treatment of advanced cancer and as such, limits for nitrosamines in the finished product would be set in line with ICH Q3B. The MAA is requested to submitting a consolidated risk evaluation by end of March 2021 and to conduct confirmatory testing of finished product by end of year 2021. This is considered acceptable given the posology and advanced cancer indication. The benefit/risk of the product is considered positive despite this outstanding issue which will be addressed post-approval.

### 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

### 2.2.6. Recommendations for future quality development

The applicant commits to submit a consolidated Nitrosamines risk evaluation further considering all of the aspects mentioned in the product specification in section 2.2.3 by end of March 2021, and to conduct confirmatory testing of finished product by end of year 2021.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of sunitinib are well known. As sunitinib is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. The overview based on literature review is, thus, appropriate. 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. Discussion on impurity profile of drug substance and drug product has not been provided. Following the quality assessment, no concerns of toxicological importance have been identified for drug substance specification. 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

Justification that introduction of Sunitinib Accord hard capsules is considered unlikely to result in any significant increase in the combined sales volumes for all sunitinib containing products and the exposure of the environment to the active substance based on generic nature of the product has been provided. This is sufficient.

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Sunitinib Accord manufactured by Accord Healthcare S.L.U. is considered unlikely to

result in any significant increase in the combined sales volumes for all sunitinib containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

### 2.3.3. Discussion on non-clinical aspects

Justification provided by the applicant that the introduction of Sunitinib Accord hard capsules is considered unlikely to result in any significant increase in the combined sales volumes for all sunitinib containing products and the exposure of the environment to the active substance is acceptable. Thus, the ERA is expected to be similar and not increased.

### 2.3.4. Conclusion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of sunitinib are well known. There are no concerns from non-clinical perspective.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

This is an application for hard capsules containing sunitinib. To support the marketing authorisation application the applicant conducted 3 bioequivalence studies with cross-over design under fasting / fed conditions. These studies were pivotal studies for the assessment.

The applicant has provided a clinical overview where pharmacology, efficacy and safety of sunitinib were discussed. The active substance of Sunitinib Accord 12,5 mg (25 mg, 37,5 mg, 50 mg) hard capsules is not considered a new active substance. Pharmacodynamic, pharmacokinetic, efficacy and safety profiles of sunitinib are well known. As sunitinib is a widely used, well-known active substance, no further studies are required. An overview based on literature review is, thus, appropriate. Information stated in the clinical overview is up-to-date and adequately supported with the scientific literature.

The proposed indication and posology of test product are in line with the reference product Sutent.

### *GCP*

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

### *Exemption*

Biowaiver is applied for the lower strengths of 12.5, 25 and 37.5 mg capsules.

In accordance with the 'Guideline on the investigation of bioequivalence' EMA CPMP/EWP/QWP/1401/98 Rev. 1/corr**, if the application concerns several strengths of the active substance, a bioequivalence study investigating only one strength may be acceptable if all the following conditions are fulfilled:

a) The pharmaceutical products are manufactured by the same manufacturing process.

b) The qualitative composition of the different strengths is the same.

c) The composition of the strengths is quantitatively proportional i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate

release products, coating components, capsule shell, colour agents and flavours are not required to follow this rule).

d) Appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

According to the SmPC of the innovator product the area under the plasma concentration-time curve (AUC) and Cmax increase proportionally with dose in the dosing ranges of 25 to 100 mg. Additionally, the lower therapeutic dose is 25 mg, while the 12.5 mg strength is used for dose adjustments in 12.5 mg steps, based on individual safety and tolerability. Therefore, although an additional 12.5 mg strength is available this is administered to subjects in order to modify their current dose at a total dose lying within the linear dose range. Further to the above, Sunitinib hard capsules 12.5, 25, 37.5 and 50 mg product-specific bioequivalence adopted guidance as published by the EMA authorities (EMA/CHMP/315233/2014) suggests that the bioequivalence study should be conducted on the highest strength of 50 mg, provided that all biowaiver conditions are fulfilled for the lower strengths.

According to sunitinib product-specific guidance (EMA/CHMP/315233/2014), the pharmacokinetics for sunitinib is linear, thus, in principle, the biowaiver request for the additional lower strengths is applicable.

The justification for request of biowaiver is acceptable.

### *Clinical studies*

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

## 2.4.2. Pharmacokinetics

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

**BIOEQUIVALENCE STUDY (2134):** A Single-Dose, Randomized, Open-Label, Two-Way Crossover, Pivotal, Bioequivalence Study of Sunitinib 50 mg Capsules and Sutent 50 mg Hard Capsules (Pfizer Ltd., UK) in Healthy Male Volunteers under Fasting Conditions.

### *Methods*

| | |
|---|---|
| CRO | **Clinical, Pharmacokinetic and Statistical:**<br>BioPharma Services Inc.<br>4000 Weston Road,<br>Toronto, Ontario, Canada, M9L3A2<br>**Bioanalytical:**<br>Anapharm Europe, S.L.U.<br>Encuny 22, 2nd floor 08038<br>Barcelona, Spain |
| Protocol identification No. | BPSI Protocol Number: 2134 |
| Clinical Phase: | Clinical study initiation: 22 June, 2017<br>Clinical study completion: 31 July, 2017 |

| | |
|---|---|
| Bioanalytical Phase: | 24/07/2017 – 04/08/2017 |

## *Study design*

This was a pivotal, single-dose, randomised, open-label, two-period, two-sequence, two-treatment, single-centre, two-way crossover study designed to demonstrate comparative bioavailability of sunitinib from Sunitinib 50 mg Capsules and Sutent 50 mg Hard Capsules administered to healthy male subjects under fasting conditions. Subjects were randomly assigned to one of the two dosing sequences.

| | Period 1 | Period 2 |
|---|---|---|
| Sequence 1 | T | R |
| Sequence 2 | R | T |

Subjects took their assigned formulation, designated by the randomisation scheme, after at least a 10-hour fast, with 240 ±3 mL of ambient temperature water at their scheduled timepoint. Subjects were instructed not to touch, chew, bite or break the study drug.

Following a fasting period of at least 4 hours after dosing, subjects were given standardised meals and caffeine/methylxanthine-free beverages were provided at approximately 4.5, 9.5 and 13.5 hours after dosing in each period. With the exception of the water ingested during drug administration, water was not permitted from 1 hour prior to drug administration until 1 hour post-dose, after which water was permitted ad libitum.

Blood samples were taken at the following time points: Pre-dose and at 1, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 13, 14, 16, 24, 36, 48 and 72 hours after dosing in each study period.

The washout interval between drug administrations was 21 days, this is adequate.

## *Test and reference products*

The following table presents information on the study drugs:

| Treatment Code | T | R |
|---|---|---|
| Drug Name: | Sunitinib | Sutent® |
| Lot No.: | 7XE02 / 72361 | 650DB |
| Strength: | 50 mg | 50 mg |
| Dosage Form: | Capsules | Hard Capsules |
| Manufactured by/for: | | Pfizer Ltd., UK |
| Potency: | 100.6 % | 99.2 % |
| Manufacturing Date: | 04/2017 | Not Applicable |
| Expiry Date: | 10/2017 | 08/2019 |
| Dose: | 1 x 50 mg | 1 x 50 mg |

The batch size of the test product was 100 000 capsules.

## *Population(s) studied*

The subjects were healthy male volunteers between 23 – 62 years of age with body mass index (BMI) between 18,5 – 29,7 kg/m2.

Ethnicity was following: 11 subjects White, 7 subjects Black, 1 subject Asian, 1 subject Native American and 3 subjects Hispanic/Latino.

Twenty-four subjects participated in the study of which 23 subjects completed the study. Subject 23 voluntarily withdrew due to personal reasons prior to period 2.

## *Results*

Twenty-four (24) subjects were dosed at the start of the study, of which twenty-three (23) subjects completed the study in its entirety.

**Table 1: Pharmacokinetic parameters for sunitinib under fasting conditions (non-transformed values; arithmetic mean ± SD, tmax median, range)**

| **Treatment** | **$AUC_{0-72}$** **ng/ml/h** | **$AUC_{0-\infty}$** **ng/ml/h** | **$C_{max}$** **ng/ml** | **$t_{max}$** **h** |
|---|---|---|---|---|
| **Test (N=23)** | 1126.07 ± 285.57 | 1521.96 ± 426.29 | 31.88 ± 7.78 | 6.00 (5.00 – 12.00) |
| **Reference (N=23)** | 1144.58 ± 302.61 | 1567.88 ± 450.33 | 32.22 ± 8.02 | 6.73 (5.00 – 10.00) |
| ***Ratio (90% CI)** | 100.58% (97.07%, 104.21%) | 97.35% (90.96%, 104.19%) | 98.46% (89.99%, 107.74%) | |

**$AUC_{0-72}$** Area under the plasma concentration curve from administration to last observed concentration at time 72 hours.

**$AUC_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time.

$AUC_{0-\infty}$ does not need to be reported when $AUC_{0-72h}$ is reported instead of $AUC_{0-t}$

**$C_{max}$** Maximum plasma concentration

**$t_{max}$** Time until Cmax is reached

Bioequivalence was demonstrated between the test Sunitinib Accord 50 mg Capsules and reference Sutent 50 mg Hard Capsules in healthy male volunteers under fasted conditions for sunitinib.

## *Safety*

A total of 11 mild AEs were experienced by the subjects after taking the Test product (6x somnolence, 3x headache, 1x diarrhoea and 1x abnormal semen viscosity).

A total of 11 mild AEs were experienced by the subjects after taking the Reference product (8x somnolence, 1x blepharitis, 1x headache and 1x nausea). No AE associated with clinical laboratory tests was experienced by the subjects at post-study. No serious adverse events were reported during the conduct of this study. There were no deaths reported during the conduct of the study**.**

**BIOEQUIVALENCE STUDY (2135):** A Single-Dose, Randomized, Open-Label, Two-Way Crossover, Pivotal, Bioequivalence Study of Sunitinib 50 mg Capsules and Sutent 50 mg Hard Capsules (Pfizer Ltd., UK) in Healthy Male Volunteers under Fed Conditions.

## *Methods*

| | |
|---|---|
| CRO | **Clinical, Pharmacokinetic and Statistical:**<br>BioPharma Services Inc.<br>4000 Weston Road,<br>Toronto, Ontario, Canada, M9L3A2<br><br>**Bioanalytical:**<br>Anapharm Europe, S.L.U.<br>Encuny 22, 2nd floor 08038<br>Barcelona, Spain |
| Protocol identification No. | BPSI Protocol Number: 2135 |
| Clinical Phase: | Clinical study initiation: 22 June, 2017<br>Clinical study completion: 31 July, 2017 |
| Bioanalytical Phase: | 26/07/2017 – 03/08/2017 |

## *Study design*

This was a pivotal, single-dose, randomised, open-label, two-period, two-sequence, two-treatment, single-centre, two-way crossover, comparative bioavailability study of Sunitinib 50 mg Capsules and Sutent 50 mg Hard Capsules. The products were studied using a two-way crossover design with 24 healthy male non-smoking (for at least 6 months prior to first drug administration) volunteers being administered an oral dose of 1 × 50 mg Capsules under fed conditions.

| | Period 1 | Period 2 |
|---|---|---|
| Sequence 1 | T | R |
| Sequence 2 | R | T |

Subjects were confined to clinical facility from at least 10.5 hours prior to each drug administration until after the 24-hour blood sample collection in each study period.

In each period, an optional snack was provided to each subject after check-in and prior to the fasting period. Subjects fasted for at least 10 hours prior to the start of the high-fat, high-calorie breakfast and for at least 4 hours following each drug administration. Subjects were served a high-fat, high-calorie breakfast 30 minutes prior to drug administration. Subjects were required to finish the meal in 30 minutes or less; however, the drug product was administered 30 minutes after start of the high fat/high calorie breakfast.

The high-fat high-calorie breakfast consisted of the following (the nutrition values stated are approximate values):

| Meal content | Amount (g) | Energy (kcal) | Protein (kcal) | Carbohydrates (kcal) | Fat (kcal) |
|---|---|---|---|---|---|
| 2 Large Eggs | 106 | 140 | 48 kcal (12g) | 8 kcal (2g) | 90 kcal (10g) |
| 2 Slices of Toast (white bread) | 60 | 140 | 20 kcal (5g) | 112 kcal (28g) | 13.5 kcal (1.5g) |
| 2 Tablespoons of Butter | 28 | 206 | 0.96 kcal (0.24g) | 0.08 kcal (0.02g) | 210 kcal (23.34g) |
| 120g of Hash Brown Patties | 120 | 240 | 8 kcal (2g) | 120 kcal (15g) | 126 kcal (14g) |
| 2 Slices of Bacon (Baked) | 16 | 88 | 23.1 kcal (5.78g) | 0.9 kcal (0.22g) | 63 kcal (7g) |
| 240 mL Whole Milk | 247.2 | 151 | 31.2 kcal (7.8g) | 47.6 kcal (11.9g) | 72.5 kcal (8.05g) |
| **TOTAL** | **577.2g** | **965 kcal** | **131.26 kcal** | **288.58 kcal** | **575 kcal** |
| **%** | | | **13.60%** | **29.90%** | **59.59%** |

Following a fasting period of at least 4 hours after dosing, subjects were given standardised meals and caffeine/methylxanthine-free beverages at approximately 4.5, 9.5 and 13.5 hours after dosing in each period. Meals and beverages during confinement were identical between each study period.

No food was allowed from at least 10 hours before the EMA-recommended high-fat, high-calorie breakfast. With the exception of the water ingested during drug administration and the fluids served with breakfast, no fluid was permitted from 1 hour prior to drug administration until 1 hour post-dose, after which water was permitted ad libitum.

Blood samples were taken at the following time points: Pre-dose and at 1, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 13, 14, 16, 24, 36, 48 and 72 hours after dosing in each study period.

The washout interval between drug administrations was 21 days.

The following table presents information on the study drugs:

| Treatment Code | T | R |
|---|---|---|
| Drug Name: | Sunitinib | Sutent® |
| Lot No.: | 7XE02 / 72361 | 650DB |
| Strength: | 50 mg | 50 mg |
| Dosage Form: | Capsules | Hard Capsules |
| Manufactured by/for: | | Pfizer Ltd., UK |
| Potency: | 100.6 % | 99.2 % |
| Manufacturing Date: | 04/2017 | Not Applicable |
| Expiry Date: | 10/2017 | 08/2019 |
| Dose: | 1 x 50 mg | 1 x 50 mg |

The batch size of the test product was 100 000 capsules.

## *Population(s) studied*

The subjects were healthy male volunteers between 23 – 62 years of age with body mass index (BMI) between 21,4 – 29,8 kg/m2.

Ethnicity was following: 5 subjects White, 9 subjects Black, 4 subjects Asian and 6 subjects Hispanic/Latino.

Twenty-four (24) subjects were dosed at the start of the study, of which nineteen (19) subjects completed the study in its entirety.

Subject 02 voluntarily withdrew due to personal reasons prior to period 2 check-in.

Subject 03 voluntarily withdrew prior to period 2 check-in.

Subject 04 was dismissed at Period 2 check-in due to Positive Cotinine Test.

Subject 11 was dismissed at Period 2 check-in due to Positive DOA (Benzodiazepines) Test.

Subject 13 was dismissed due to AEs (Rash and Pruritus) prior to Period 2 check-in.

## *Results*

Twenty-four (24) subjects were dosed at the start of the study, of which nineteen (19) subjects completed the study in its entirety.

**Table 2: Pharmacokinetic parameters for sunitinib under fed conditions (non-transformed values; arithmetic mean ± SD, tmax median, range)**

| Treatment | $AUC_{0-72}$ ng/ml/h | $AUC_{0-\infty}$ ng/ml/h | $C_{max}$ ng/ml | $t_{max}$ h |
|---|---|---|---|---|
| **Test (N=19)** | 1260.52 ± 320.34 | 1743.19 ± 461.28 | 32.96 ± 9.28 | 10.50 (6.00 – 16.00) |
| **Reference (N=19)** | 1252.59 ± 197.19 | 1754.69 ± 298.91 | 33.50 ± 7.28 | 10.00 (6.00 – 16.00) |
| ***Ratio (90% CI)** | 94.98% (80.84%, 111.59%) | 93.75% (79.09%, 111.13%) | 92.56% (77.42%, 110.65%) | |

**$AUC_{0-72}$** Area under the plasma concentration curve from administration to last observed concentration at time 72 hours.

**$AUC_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time.

$AUC_{0-\infty}$ does not need to be reported when $AUC_{0-72h}$ is reported instead of $AUC_{0-t}$

**$C_{max}$** Maximum plasma concentration

**$t_{max}$** Time until Cmax is reached

Bioequivalence was not demonstrated between the test Sunitinib Accord 50 mg Capsules and reference Sutent 50 mg Hard Capsules in healthy male volunteers under fed conditions for sunitinib.

## *Safety*

A total of 27 adverse events involving 13 subjects in this study.

No serious AEs were reported during the conduct of this study.

There were 16 AEs associated with 9 subjects who received Treatment T (5x somnolence, 2x milia, 1x abdominal distension, 1x cough, 1x fatigue, 1x headache, 1x hypertension, 1x nausea, 1x ocular hyperaemia, 1x pruritus and 1x rash).

There were 8 AEs associated with 8 subjects who received Treatment R (2x headache, 2x somnolence, 1x bradycardia, 1x fatigue, 1x hypertension and 1x paraesthesia).

There were no deaths reported during the conduct of the study.

**BIOEQUIVALENCE STUDY (17-VIN-0703):** An open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study of Sunitinib 50 mg capsule and SUTENT (Sunitinib) 50 mg hard capsules of Pfizer Ltd., United Kingdom in healthy, adult, male subjects under fed conditions.

## *Methods*

| | |
|---|---|
| CRO | **Clinical, Pharmacokinetic and Statistical:**<br>Veeda Clinical Research Pvt. Ltd.<br>Shivalik Plaza, Near I.I.M.,<br>Ambawadi<br>Ahmedabad – 380 015,<br>India<br><br>**Bioanalytical:**<br>Veeda Clinical Research Pvt. Ltd.,<br>Rev. Sur. No. 12/1, Insignia,<br>Corporate House, Nr. Grand Bhagvati Hotel,<br>Sindhu Bhavan Road,<br>S. G. Highway, Bodakdev,<br>Ahmedabad, 380054, Gujarat, India. |
| Protocol identification No. | Project No.: 17-VIN-0703 |
| Clinical Phase: | 15 Sep 2017 to 11 Oct 2017 |
| Bioanalytical Phase: | 04 Oct 2017 to 15 Oct 2017 |

## *Study design*

This was an open label, balanced, randomised, two-treatment, two-sequence, two-period, single dose, crossover oral bioequivalence study of Sunitinib 50 mg capsule and SUTENT (Sunitinib) 50 mg hard capsules of Pfizer Ltd., United Kingdom in healthy, adult, male subjects under fed conditions.

| Group | Clinical phase | Admission | Dosing | Discharge | Completion date |
|---|---|---|---|---|---|
| Group 01 (Subjects 01 to 46[@]) | Period 01 | 15 Sep 2017 | 16 Sep 2017 | 18 Sep 2017 | 19 Sep 2017 |
| | Period 02 | 06 Oct 2017 | 07 Oct 2017 | 09 Oct 2017 | 10 Oct 2017 |
| Group 02 (Subjects 47-50, 1028, 1038, 1040, 1042, 1043, 1044) | Period 01 | 16 Sep 2017 | 17 Sep 2017 | 19 Sep 2017 | 20 Sep 2017 |
| | Period 02 | 07 Oct 2017 | 08 Oct 2017 | 10 Oct 2017 | 11 Oct 2017 |

[@]Subject no 1028, 1038, 1040, 1042, 1043, 1044 were enrolled in Group 02.

Subjects were confined in the clinical facility of Veeda Clinical Research Pvt. Ltd., to ensure 10.00 hrs overnight fasting before scheduled start time of a high-fat high-calories breakfast and continued to be housed in the facility till 48.00 hours post-dose in each study period. The subjects received breakfast consisting of high-fat and high-calorie (approximately 800-1000 calorie) 30 minutes prior to administration of the study drug formulation.

Subjects were again reported to the clinical facility for 72.00 hours ambulatory blood sample and safety assessment in each period.

| BREAKFAST BEFORE DOSING |
|---|
| Cheese Sandwich -80gm |
| Whole Milk - 240ml |
| Egg Omelet (Plain) - 80gm |
| Chicken Fry - 40gm |
| Potato Fry - 22gm |
| Tomato Chutney - 20ml |

| Food items | | Amount | CHO | Protein | Fat | Calories |
|---|---|---|---|---|---|---|
| | | gm | gm | gm | gm | kcal |
| Cheese Sandwich - | Bread | 50 | 29.00 | 3.20 | 0.60 | 134.30 |
| | Cheese | 30 | 1.96 | 7.20 | 7.36 | 102.80 |
| Whole Milk - | Milk | 240ml | 12.00 | 7.92 | 14.40 | 209.28 |
| | Sugar | 5 | 5.00 | 0.00 | 0.00 | 20.00 |
| Egg Omelet (Plain) - | Eggs | 80(2no.) | 0.00 | 10.64 | 10.64 | 138.30 |
| | Butter | 5 | 0.00 | 0.00 | 4.05 | 36.45 |
| Chicken Fry - | Chicken | 40 | 0.00 | 10.36 | 0.24 | 43.60 |
| | Oil | 10ml | 0.00 | 0.00 | 10.00 | 90.00 |
| Potato Fry - | Potato | 75 | 16.95 | 1.20 | 0.08 | 73.28 |
| | Oil | 15ml | 0.00 | 0.00 | 15.00 | 135.00 |
| Tomato chutney | | 20ml | 0.50 | 0.10 | 0.19 | 4.11 |
| | | | | | | |
| Total (gm-approx) | | | 65.41 | 40.62 | 62.56 | |
| Total (Calories) | | | 261.64 | 162.48 | 563.00 | 987.12 |
| % | | | 26.51 | 16.46 | 57.03 | 100.00 |

(1gram carbohydrate and protein is equal to 4 kcal and 1gram of fat is equal to 9 kcal)

Subjects received a standard meal at about 4, 8, 12, 24, 28, 32 and 36 hours after dosing in each study period.

A total of 27 blood samples were collected during each study period.

The pre-dose blood sample of 3.0mL (0.00 hr) was collected within one hour prior to schedule dosing time. The post-dose blood samples of 3.0mL each were drawn at 1.00, 3.00, 4.00, 5.00, 6.00, 6.50, 7.00, 7.50, 8.00, 8.50, 9.00, 9.50, 10.00, 10.50, 11.00, 11.50, 12.00, 12.50, 13.00, 14.00, 16.00, 20.00, 24.00, 36.00, 48.00 and 72.00 hours after dosing in each study period.

The washout interval between drug administrations was 21 days.

## *Test and reference products*

| | | |
|---|---|---|
| Test Product (T): | Formulation | Sunitinib 50 mg capsules |
| | Manufactured for | |
| | Lot No. | 7XE02/72361 |
| | Manufacturing Date | Apr 2017 |
| | Expiry/Retest Date | Oct 2017 |

| | | |
|---|---|---|
| Reference Product (R): | Formulation | Sutent® 50 mg hard capsules |
| | Marketing Authorization Holder | Pfizer Ltd, United Kingdom |
| | Lot No. | 650DB |
| | Manufacturing Date | NA |
| | Expiry Date | Aug 2019 |

## *Population(s) studied*

The subjects were healthy male Asian volunteers between 22 – 42 years of age with body mass index (BMI) between 19 – 29,5 kg/m2.

A total of 50 (+07 extra) healthy, adult, human male subjects were enrolled (Two groups)

In group 01: 40 (Subject no. 01 to 46) healthy, adult, human male subjects were enrolled.

In group 02: 10 (Subject no. 47-50, 1028, 1038, 1040, 1042, 1043, 1044 + 01 extra subjects) healthy, adult, human male subjects were enrolled.

Subject number 28, 38, 40, 42, 43 and 44 withdrawn due to AE before dosing (not dosed) on 16 Sep 2017 in period 01, hence subjects were withdrawn from the study in group 01 and replaced with extra subjects (Ex-01, Ex-02, Ex-03, Ex-04, Ex-05 and Ex-06) in group 02 and given the subject number 1028, 1038, 1040, 1042 and 1044 respectively.

Subject number 48 withdrawn due to AE before dosing (not dosed) on 17 Sep 2017 in period 01, hence subjects were withdrawn from the study in group 02 and replaced with extra subject (Ex-07) and given the subject number 1048.

Following subjects were withdrawn from the study:

Group 01:

• Subject no. 10 was withdrawn due to AE after dosing of period 01 on 16 Sep 2017, hence withdrawn from the study.

• Subject no. 27 did not report to facility during admission of period 02 on 06 Oct 2017, hence withdrawn from the study.

• Subject no. 32 withdrew consent on 06 Oct 2017 in period 02, hence withdrawn from the study.

Group 02:

• Subject no.49 did not complete high fat, high calorie breakfast on 17 Sep 2017 in period 01, hence withdrawn from the study.

Hence, a total 46 subjects completed the study as per the protocol.

## *Results*

In accordance with the study protocol, 50 subjects were enrolled in the study and data from 46 subjects were used for pharmacokinetic and statistical analyses.

**Table 3: Pharmacokinetic parameters for sunitinib under fed conditions (non-transformed values; arithmetic mean ± SD, tmax median, range)**

| **Treatment** | **$AUC_{0-72}$** ng/ml/h | **$AUC_{0-\infty}$** ng/ml/h | **$C_{max}$** ng/ml | **$t_{max}$** h |
|---|---|---|---|---|
| **Test (N=46)** | 950.64 ± 179.66 | 1270.97 ± 283.32 | 24.04 ± 5.16 | 10.50 (3.00 – 24.00) |
| **Reference (N=46)** | 950.56 ± 220.24 | 1294.01 ± 348.29 | 24.13 ± 5.70 | 9.75 (5.00 – 24.00) |
| ***Ratio (90% CI)** | 101.07% (97.59%, 104.67%) | *Not calculated* | 100.00% (96.17%, 103.98%) | |

**$AUC_{0-72}$** Area under the plasma concentration curve from administration to last observed concentration at time 72 hours.
**$AUC_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when $AUC_{0-72h}$ is reported instead of $AUC_{0-t}$
**$C_{max}$** Maximum plasma concentration
**$t_{max}$** Time until Cmax is reached

*ln-transformed values

The study meets the bioequivalence criteria as 90% confidence intervals for geometric least square mean ratio of (T/R) for the ln-transformed parameters $C_{max}$ and $AUC_{0-72}$ are within the acceptance range of 80.00% - 125.00%.

## *Safety*

Seven subjects (Subject no. 28, 38, 40, 42, 43, 44, and 48) reported adverse event before period 01 dosing. Three subjects (Subject no. 06, 07 and 20) reported adverse event after administration of reference product (R). Six subjects (Subject no. 07, 10, 13, 26, 29 and 30) reported adverse event after administration of test product (T). Subject no. 03 reported adverse event as clinically significant laboratory value (Asymptomatic increase in SGOT) and subject no.1028 reported adverse event (QTc prolongation) during safety assessment after administration of Reference product (R).

There were no deaths reported during the conduct of the study.

**POOLED ANAYSIS FOR FED STUDIES (17-VIN-0889):** Title: Pooled statistical analysis between two, open label, balanced, randomised, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence studies of Sunitinib 50 mg capsule and SUTENT (Sunitinib) 50 mg hard capsules of Pfizer Ltd., United Kingdom in healthy, adult, male subjects under fed conditions. (dated 28/11/2017)

**Statistical Method**

The statistical analysis plan mentioned in the protocol was used to analyse the data. Dataset for estimation of pharmacokinetic parameters Cmax, AUC0-72, Tmax, AUC0-inf, AUCt/AUCinf, λz and t1/2 were planned to calculate using non-compartmental model by using Phoenix WinNonlin Version 7.0 (Pharsight Corporation, USA).

For Sunitinib, ln-transformed pharmacokinetic parameters Cmax and AUC0-72 were planned to analyse by analysis of variance (ANOVA) using PROC GLM in SAS Software, Version 9.4.

The model statement of PROC GLM in SAS Software included the fixed effects of Sequence, Treatment, Period and subject (Sequence). The Sequence effect was planned to test using the Subject (Sequence) effect as the error term. The sequence effect was planned to test at the 0.10 level of significance and other main effects related to treatment and period were planned to test at the 0.05 level of significance.

Ninety percent confidence intervals for the difference between least square means of test and reference formulations were planned to calculate using mean square error, obtained in ANOVA, for ln-transformed Cmax and AUC0-t for Sunitinib. Ninety percent confidence interval for the geometric least squares mean ratio was planned to obtain by taking the exponent of lower and upper limits of 90% confidence interval, obtained for the least square mean difference.

Two one-sided tests, namely Schuirmann's tests, was employed at 5% level of significance for the lower and upper limits of 90% confidence interval to check whether the 90% confidence interval for Cmax and AUC0-72 for Sunitinib were entirely within the bioequivalence limits 0.80 - 1.25 (80.00% - 125.00%). However, the bioequivalence assessment was based on the 90% CI for the primary pharmacokinetic parameters Cmax and AUC0-72.

**Results**

Final statistical analysis datasets for 17-VIN-0703 and 2135 studies were consisted of 46 and 19 subjects respectively, therefore pooled pharmacokinetic and statistical analyses was performed over a total of 65 subjects.

**Table 4: Pharmacokinetic parameters for sunitinib under fed conditions based on pooled data (non-transformed values; arithmetic mean ± SD, tmax median, range)**

| Treatment | $AUC_{0-72}$ ng/ml/h | $AUC_{0-\infty}$ ng/ml/h | $C_{max}$ ng/ml | $t_{max}$ h |
|---|---|---|---|---|
| **Test (N=65)** | 1041.92 ± 267.65 | 1412.15 ± 410.17 | 26.65 ± 7.73 | 10.50 (3.00 – 24.00) |
| **Reference (N=65)** | 1040.08 ± 253.43 | 1427.23 ± 391.98 | 26.87 ± 7.50 | 10.00 (5.00 – 24.00) |
| ***Ratio (90% CI)** | 99.31% (94.37%, 104.51%) | *Not calculated* | 97.90% (92.48%, 103.64%) | |

**$AUC_{0-72}$** Area under the plasma concentration curve from administration to last observed concentration at time 72 hours.
**$AUC_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when $AUC_{0-72h}$ is reported instead of $AUC_{0-t}$

| | |
|---|---|
| $C_{max}$ | Maximum plasma concentration |
| $t_{max}$ | Time until Cmax is reached |

***In-transformed values***

The results of the pooled analysis are considered of minor relevance for this application and are supportive only.

### *Conclusions*

Bioequivalence between test product Sunitinib Accord 50 mg capsules and the reference product Sutent 50 mg hard capsules with respect to rate and extent of absorption of sunitinib has been shown under fasting condition.

Due to different salt used in Sunitinib Accord compared to reference product Sutent, studies for food effect with the highest strength (therapeutic dose) were also conducted. In Study 2135, bioequivalence under fed conditions was not demonstrated probably due to one subject with low exposure for the test product and small sample size (n=24 subjects). However, in Study 17-VIN-0703 (same design as Study 2135) where more subjects (n=50) were recruited bioequivalence under fed conditions was demonstrated. In addition, the pooled analysis for Studies 2135 and 17-VIN-0703 showed bioequivalence between the test and the reference product under fed condition.

The results of the bioequivalence study with the 50 mg formulation can be extrapolated to the other strengths 12,5 mg (25 mg, 37.5 mg) according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

## 2.4.3. Pharmacodynamics

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

## 2.4.4. Post marketing experience

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

## 2.4.5. Discussion on clinical aspects

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

The study 2134 demonstrated bioequivalence between the test Sunitinib Accord 50 mg Capsules and reference Sutent 50 mg under fasting conditions.

The solubility study between sunitinib base and sunitinib malate (carried out using the shake-flask method) demonstrated that the solubility of Sunitinib base is highly pH-dependent. More specifically, Sunitinib base showed very poor solubility in pH 6.8 phosphate buffer, lower than 1X, while on the other hand, Sunitinib malate exhibited more than 10X solubility in all pH range of 1.0 to 6.8.

Given the above results indicating marked differences between originator malate salt and test sunitinib base in higher pH 6.8 conditions, the applicant decided to additionally conduct a fed study in order to confirm comparability "with and without food" and thus to be in line with the administration conditions documented in the SmPC of Sutent.

As such, two bioequivalence studies (one of them failed to demonstrate bioequivalence) were also conducted in order to compare the bioavailability of sunitinib from Sunitinib Accord 50 mg hard capsules and Sutent 50 mg hard capsules in healthy male volunteers under fed conditions.

For Study 0703, the applicant considered ANOVA model which took into account that there were two groups of subjects which underwent study in different time periods. This ANOVA model included fixed effects group, sequence, sequence by group, formulation by group and period (within group) and random effect subject nested within sequence. Such model resembles ANOVA model for two-stage design which proceeded to second stage where group is equivalent to stage. According to Questions & Answers: positions on specific questions addressed to the Pharmacokinetics Working Party (EMA/618604/2008 Rev. 11), section Number of subjects in a two-stage bioequivalence study design, such ANOVA model should not include interaction formulation by group and random effect of subject nested within sequence by group should be rather fixed effect. During the evaluation procedure the applicant was asked to re-evaluate BE based on ANOVA model without interaction formulation by group and with inclusion of subject nested within sequence by group as fixed effects. The applicant provided the required data therefore the issue was resolved.

### 2.4.6. Conclusions on clinical aspects

Based on the presented results of bioequivalence studies Sunitinib Accord 50 mg hard capsules (12,5 mg; 25 mg; 37,5 mg) is now considered bioequivalent with Sutent 50 mg hard capsules (12,5 mg; 25 mg; 37,5 mg) under fast and fed conditions.

## *2.5. Risk management plan*

### *Safety concerns*

**Table 5: Summary of the safety concerns**

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | Cardiotoxicity<br>• Torsade de pointes<br>• Left ventricular dysfunction/Heart Failure<br>• Pericardial events<br>• Cardiac ischaemic events<br>Reversible posterior Leukoencephalopathy syndrome<br>Hepatic failure<br>Osteonecrosis of the jaw<br>• Severe Cutaneous Adverse Reactions<br>Renal failure |
| Important potential risks | Carcinogenicity |
| Missing information | Severe hepatic impairment |

### *Pharmacovigilance plan*

Routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures in line with the reference product.

### *Risk minimisation measures*

Routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

### *Conclusion*

The CHMP and PRAC considered that the risk management plan version 1.1, dated 27 February 2020, is acceptable.

## *2.6. Pharmacovigilance*

### *Pharmacovigilance system*

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

### *Periodic Safety Update Reports submission requirements*

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

## *2.7. Product information*

### 2.7.1. User consultation

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

# 3. Benefit-risk balance

This application concerns a generic version of sunitinib in hard capsules. The reference product Sutent is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after failure of imatinib treatment due to resistance or intolerance; for the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults; for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults.

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.

The bioequivalence study forms the pivotal basis with an open label, balanced, randomised, two-treatment, two-sequence, two-period, single-dose, crossover trial. 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 Sunitinib Accord met the protocol-defined criteria for bioequivalence when compared with Sutent. The point estimates and their 90% confidence intervals for the parameters

$AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$ were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

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

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

# 4. Recommendation

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

Sunitinib Accord is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after failure of imatinib treatment due to resistance or intolerance.
Sunitinib Accord is indicated for the treatment of advanced/metastatic renal cell carcinoma (MRCC) in adults.
Sunitinib Accord is indicated for the treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours (pNET) with disease progression in adults.

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 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.

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.*

Not applicable.