22 April 2022

EMA/CHMP/697928/2022

Committee for Medicinal Products for Human use (CHMP)

Withdrawal Assessment report

Sevsury

International non-proprietary name: surufatinib

Procedure No. EMEA/H/C/005728/0000

Note

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

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Administrative information

Invented name of the medicinal product:	Sevsury
INN of the active substance:	Surufatinib
Applicant:	Hutchmed Europe B.V.
Applied Indication:	Treatment of adult patients with low or intermediate grade (grade 1 [G1] or grade 2 [G2]) progressive neuroendocrine tumours of extrapancreatic or pancreatic origin that are locally advanced or metastatic.
Pharmaco-therapeutic group **(ATC Code):**	Not yet assigned
Pharmaceutical form and strength:	Hard capsules, 50 mg

List of abbreviations

Abbreviation	Definition
ADME	absorption, distribution, metabolism, and elimination
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{tau}	area under the plasma concentration-time curve from time zero to the end of the dosing interval
BA	bioavailability
BCRP	breast cancer resistance protein
BID	twice a day
BIIRC	blinded independent image review committee
BMI	body mass index
BOR	best overall response
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum observed plasma concentration
CMC	chemistry, manufacturing, and controls
C_{min}	minimum plasma concentration
CNS	central nervous system
CR	complete response
CSF1R	colony-stimulating factor-1 receptor
CSR	clinical study report
CV	cardiovasular
CYP	cytochrome P450
CYP3A4	cytochrome P450 isozyme 3A4
DCR	disease control rate
DDI	drug-drug interaction
DoR	duration of response
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
ECG	electrocardiogram
EMA	European Medicines Agency
ENETs	The European Neuroendocrine Tumour Society
epNET	extrapancreatic neuroendocrine tumors
E-R	exposure-response
ESMO	European Society for Medical Oncology

Abbreviation	Definition
EU	European Union
FDA	Food and Drug Administration
FGFR-1	fibroblast growth factor receptor-1
FLT3	fms-like tyrosine kinase
GEP	gastroenteropancreatic
G1	grade 1
G2	grade 2
G3	grade 3
GI	gastrointestinal
GLP	good laboratory practice
GMR	geometric mean ratio
ICH	International Council for Harmonisation
hERG	human *ether-à-go-go*-related gene
HMP	Hutchison MediPharma Limited
HR	hazard ratio
IC_{50}	half maximal inhibitory concentration
IDMC	Independent Data Monitoring Committee
IFN =	Interferon
IND	Investigational New Drug
MAA	Marketing Authorisation Application
MOA	mechanism of action
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NANETS	North American Neuroendocrine Tumor Society
NDA	New Drug Application
NE	not evaluable
NET	neuroendocrine tumor
OECD	Organisation for Economic Co-operation and Development
ORR	objective response rate
OS	overall survival
PBPK	physiologically based pharmacokinetic(s)
PD	pharmacodynamics(s)/progressive disease
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
pNET	pancreatic neuroendocrine tumor
popPK	population pharmacokinetic(s)
PPI	proton-pump inhibitor
PR	partial response
PRES	Posterior reversible encephalopathy syndrome

Abbreviation	Definition
PRRT	peptide-receptor radionuclide therapy
PS	performance status
QD	once daily
QTc	heart rate-corrected QT interval
QTcF	Fridericia's corrected QT interval
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RMP	risk management plan
RP2D	recommended phase 2 dose
SAE	serious adverse event
SANET	surufatinib in advanced neuroendocrine tumors
SANET-ep	Study 2015-012-00CH4
SANET-p	Study 2015-012-00CH3
SAP	statistical analysis plan
SEER	National Cancer Institute's Surveillance, Epidemiology, and End Results
SmPC	summary of product characteristics
SMQ	standardized Medical Dictionary for Regulatory Activities query
SSA	somatostatin analog
SSTR	somatostatin receptor
TCM	traditional Chinese medicine
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
t_{max}	time to reach the maximum observed plasma concentration
TSH	thyroid-stimulating hormone
TTR	time to response
ULN	upper limit of normal
US	United States
USPI	United States package insert
VEGFR	vascular endothelial growth factor receptor
WHO	World Health Organization
ΔQTcF	change from baseline in Fridericia's corrected QT interval

CHMP Recommendations

Based on the review of the data on quality, safety, efficacy, the application for Sevsury as monotherapy in the treatment of adult patients with low grade (grade 1 [G1]) or intermediate grade (grade 2 [G2]) progressive neuroendocrine tumours of extrapancreatic or pancreatic origin that are unresectable locally advanced or metastatic is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (see section VI).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Quality

GMP information is not considered sufficient.

Efficacy

The populations recruited in the SANET-ep and SANET-p trials are not representative of the European population in terms of heterogeneity and approach to medical diagnosis and prior treatments.

The major protocol amendment that changed the primary endpoint (BIIRC-PFS to INV-PFS) is not justified.

GCP compliance should be confirmed before considering approval, thus the need for a triggered GCP inspection has been raised.

Results of SANET-ep do not support the B/R of surufatinib in patients with extrapancreatic neuroendocrine tumours.

Results of SANET-p do not support the B/R of surufatinib in patients with pancreatic neuroendocrine tumours.

Questions to be posed to additional experts

NA at present

Inspection issues

GMP inspection(s)

A request for GMP inspection is required for the following site(s) in order to verify the GMP compliance status:

- *Finished product manufacturer*

The outcome of this inspection is required for the Committee to complete its examination of the application and will be needed by Day 181.

GCP inspection(s)

The applicant declared "All clinical studies included in the clinical development of surufatinib were conducted in accordance with standard operating procedures of the Sponsor and/or delegated contract research organization, which comply with the principles of Good Clinical Practice for the design, conduct, and analysis of the clinical studies. All studies were conducted under the approval of local ethics committees or institutional review boards. Before participation in the clinical studies, all subjects and patients provided informed consent. These studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the subject or patient. Where required, regulatory discussion with and approval from the appropriate health authority were obtained before study conduct."

Late protocol amendments, discrepancies in the PFS assessment, as well as other unclarities in study conduct indicate that an inspection of GCP compliance is required prior to approval.

New active substance status

Based on the review of the data, it is considered that the active substance surufatinib contained in the medicinal product Sevsury is qualified as a new active substance in itself.

Structure searches (exact search, similarity search and substructure search) have been performed using SciFinder (by Chemical Abstracts Service (CAS)), ChemSpider and PubChem. Hits from similarity search or substructure search have been elaborated. In addition, structural comparison of surufatinib with "other protein kinase inhibitors" (ATC: L01EX01, eg, sunitinib) approved in the European Union has been performed.

Surufatinib is not structurally related as a salt, ester, ether, isomer, mixture of isomers, complex or derivative of an already approved active substance(s) in the EU.

Similarity with authorised orphan medicinal products

It is considered that Sevsury is not similar to Lutathera within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Executive summary

Problem statement

Disease or condition

The applicant for Sevsury (surufatinib) has submitted a marketing authorisation application with the intention to support the following proposed indication:

> *Sevsury is indicated for the treatment of adult patients with low or intermediate grade (grade 1 [G1] or grade 2 [G2]) progressive neuroendocrine tumours of extrapancreatic or pancreatic origin that are locally advanced or metastatic.*

After a major objection on the indication was raised at the D120 LoQ, the applicant has proposed a revised version of the indication:

Sevsury is indicated for use as monotherapy for the treatment of adult patients with low grade (grade 1 [G1] or intermediate grade (grade 2 [G2]) progressive neuroendocrine tumours of extrapancreatic or pancreatic origin that are unresectable locally advanced or metastatic.

Epidemiology and risk factors

Studies of the incidence of NETs, based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, have consistently shown a marked increase in cases of NETs over the past 5 decades; the age-adjusted incidence of NETs was 1.09 per 100,000 persons in 1972 and 6.98 per 100,000 persons by 2012 (Yao 2008, Dasari 2017, Sackstein 2018). This is supported by an analysis of global epidemiologic trends, which also show growth in the incidence of NETs worldwide (Fraenkel 2014). In Europe, the incidence of NETs has also increased, and ranges between 1.33-2.33/100 000 population; however, data arise from the national and regional registries and are heterogeneous and mostly retrospective (Leoncini 2017, Hughet 2017). The increased incidence of NETs was observed for all primary tumor sites, stage, and grade. Most of the reported increase in incidence rate is thought to be due to the improvement in detection techniques (Hallet 2015).

The majority of NET cases are detected during the sixth and seventh decades of life with peak incidence and prevalence observed in patients >65 years of age (Man 2018). Men are affected slightly more frequently than women and show an adverse outcome. Most NETs are well-differentiated and occur sporadically. NETs of the pancreas, duodenum, stomach and, more rarely, NETs of the thymus and lung may also arise in the setting of the multiple endocrine neoplasia type 1 (MEN1) syndrome. Pancreatic NETs (Pan-NETs) are also associated with von Hippel-Lindau (VHL) disease, tuberous sclerosis (TSC) and neurofibromatosis. In these hereditary settings, NETs are multifocal, and the onset of disease is one to two decades earlier than in sporadic tumours. Furthermore, they are often early stage at the time of diagnosis. The frequency of a hereditary background (MEN1, VHL syndromes) was reported as 5% (Rindi 2012). Recently, whole genomic sequencing revealed 17% of apparently sporadic Pan-NETs carried germline mutations also including DNA repair genes (e.g. MUTYH, CHEK2, BRCA2) (Scarpa 2017).

Biologic features

NETs are rare tumors that arise from the diffuse neuroendocrine cell system and may occur at many different disease sites. NETs are classified based on morphology and proliferation (and, rarely, mutation spectrum) into well-differentiated NETs (G1 to G3) and poorly-differentiated neuroendocrine carcinomas (NECs), which are always G3, as seen in Table 1. These two classes of NETs reflect biologically and genetically two different diseases. When showing a high proliferation rate (>20%), there are clear prognostic differences between the two classes. Therefore, the World Health Organization (WHO) 2017 and 2019 classifications split the heterogeneous G3 GEP-NENs into well-differentiated NET G3 and poorly-differentiated NEC G3 (Kloeppel 2017, WHO Classification of Tumours 2019).

Table 1. WHO 2019 classification for NETs

Morphology	Grade	Mitotic count (2 mm^2)[a]	Ki-67 Index (%)[b]
Well-differentiated NETs	G1	<2	<3
Well-differentiated NETs	G2	2–20	3–20
Well-differentiated NETs	G3	>20	>20
Poorly-differentiated NECs • Small-cell • Large-cell	G3	>20	>20
MiNEN			
Tumour-like lesions			

HPF, high-power field; MiNEN, mixed neuroendocrine/nonendocrine neoplasm; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; WHO, World Health Organization.
[a] 10 HPF = 2 mm^2, at least 40 fields (at ×40 magnification) evaluated in areas of highest mitotic density.
[b] MIB1 antibody; percentage of 500–2000 tumour cells in areas of highest nuclear labelling.

Well-differentiated NETs that arise from the pancreas, which comprise approximately 10% of all NETs (Man 2018), are referred to as pNETs, whereas those arising from nonpancreatic tissues are referred to as epNETs. NETs arising in the tubular gastrointestinal tract and pancreas may have similar characteristics on routine histologic evaluation, but they have a different pathogenesis and biology (Duerr 2007). Pancreatic NETs in general pursue a somewhat more aggressive course than do other gastrointestinal tract NETs (Panzuto 2005), although, conversely, most systemic agents have been associated with higher response rates among patients with pancreatic NETs than in those with gastrointestinal NET.

Functionality: NETs may be classified as either functional or non-functional depending on their ability to secrete biologically active hormones and elicit characteristic symptomatology (Yehonatan 2017). Nearly all functioning NETs are well-differentiated. The classical carcinoid syndrome (watery diarrhoea, flushing, bronchospasm, hypotension, and right-sided heart disease) that results from hypersecretion of amines and peptides often facilitates diagnosis of a NET (Lips 2003).

Clinical presentation, diagnosis and stage/prognosis

The clinical presentation of NETs has evolved in more recent years. Up until two decades ago, most NETs were described as functioning and were detected following diagnostic evaluation of a hormonal syndrome. In contrast, more recent clinical series describe the majority (between 50 and 85 percent) of NETs as non-functioning (Turaga 2011). Since non-functioning tumours do not present clinically with a hormonal syndrome as compared with their functional counterparts, they often present later in the course of the disease with symptoms of local compression or metastatic disease. The majority of patients with advanced NETs have liver metastases (Riihimäki 2016). Although functionality may impact prognosis (eg, insulinomas are generally indolent tumors), the biologic behavior of most functioning NETs is defined by the grade and stage of the tumor, as it is with nonfunctioning tumors.

Histological diagnosis is mandatory in all patients and can be carried out on resection specimens or core biopsies. The neuroendocrine phenotype is proven by the IHC detection of the neuroendocrine markers synaptophysin and/or chromogranin A (CgA). As abovementioned, NET grade should be determined according to mitotic count per 2 mm^2 and Ki-67 index.

Disease stage and tumour grade are the two major independent prognostic parameters for NETs and should always be assessed. For staging, the tumour, node and metastasis (TNM) staging system proposed by the European Neuroendocrine Tumour Society (ENETS) was recently widely adopted by the eighth edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system (ESMO guidelines, Pavel 2020).

Computed tomography (CT) constitutes the basic radiological method for NET imaging because of its wide availability, standardised reproducible technique and generally high diagnostic yield. To ensure comprehensive diagnostics, CT should be contrast-enhanced and performed in arterial and venous phase. Adding MRI to CT is often necessary in order to evaluate properly the number and location of liver metastases, frequent in NETs, and to locate the sometimes very small primary tumour, especially when in the pancreas. Imaging by ^{68}Ga/^{64}Cu-DOTA-somatostatin analogue (SSA) positron emission tomography (PET) in combination with CT (PET-CT) provides high sensitivity for imaging of most types of NET lesions and should be part of the tumour staging, preoperative imaging and restaging. SSTR scintigraphy (SRS, e.g. OctreoScan™) should be carried out when PET-CT is not available but is considerably less sensitive. The strength of a PET-CT is a higher detection rate of lymph node, bone and peritoneal lesions as well as unknown primary tumours (ESMO guidelines, Pavel 2020). Tumour markers in blood (CGA, 5HIAA) should be analysed during initial evaluation and follow-up.

The prognosis of patients with NETs varies according to a number of different factors, such as the location of the primary tumor, stage, tumor differentiation and histologic proliferation rate grade (Man 2018). There is substantial variability in survival among patients with NETs originating at different primary sites (Man 2018). Tumor grade at diagnosis is also a strong predictor of survival. The 5-year survival rate is 26.1% for patients with low-grade tumors but 8.7% for those with undifferentiated high grade tumors at diagnosis (Man 2018). Furthermore, tumor stage at diagnosis is closely correlated with prognosis and survival (Halfdanarson 2008, Man 2018); the 5-year survival rate is 46.7% for patients with localized disease at diagnosis but 14.2% for those with distant metastasis (Man 2018).

Management

Due to the complexity of the disease, treatment guidelines in the EU are divided by the origin of the tumour. Guidelines from the European Society for Medical Oncology (ESMO) currently divide tumors into gastroenteropancreatic (GEP) (Pavel 2020) or bronchial and thymic origin (Baudin 2021). The European Neuroendocrine Tumour Society (ENETS) has also issued 8 guidelines covering different forms of the disease (Delle Fave 2016, Falconi 2016, Garcia-Carbonero 2016, Neiderle 2016, O'Toole 2016, Pape 2016, Pavel 2016, Ramage 2016).

Treatment options for managing locally advanced and metastatic NETs consist primarily of cytoreductive surgery, ablative procedures, and systemic antitumor therapy, including somatostatin analogs (SSAs)(widely used but approval as antiproliferative agents limited to gastroenteropancreatic [GEP] NETs), everolimus, sunitinib (limited to pNETs only), ^{177}Lu-DOTATATE (widely used but approval limited to G1-2 GEP NETs), interferon-alpha (although approved for 'carcinoid tumours') and chemotherapy (especially for pNETs and lung NETs). Watchful waiting can be used for patients with indolent or low burden disease, no symptoms and/or in patients with contraindications to active therapy.

In a comprehensive and multidisciplinary treatment setting, patients with NETs can be treated with different interventional techniques, especially for liver metastases, among which radical and debulking operations are highlighted. In rare cases, liver transplantation can be also considered. Moreover, other liver-directed therapies can be used (RFA, TAE, TACE, SIRT, brachytherapy, stereotactic RT). Locoregional therapies for lung NETs include RFA, cryoablation, endobronchial treatment and (stereotactic) RT."

Somatostatin analogues (SSAs): SSAs (octreotide, lanreotide) are an established antiproliferative therapy in first-line for functioning metastatic NETs. The PROMID study showed prolongation of time to tumour progression (TTP) in therapy-naive advanced metastatic midgut NETs (mostly G1 and with low tumour burden) by 8.3 months; TTP with octreotide LAR 30 mg was 14.3 months and 6 months with placebo (Rinke 2009). The CLARINET study demonstrated efficacy not only in midgut but also in pNETs

and NETs with high liver tumour burden (>25%), and NET G2 with a Ki-67 of ≤10%. Most patients (96%) had stable disease at study onset. The median progression-free survival (mPFS) was not reached with lanreotide (>27 months) and was 18 months in the placebo arm in the initial publication (Caplin 2014), but the final mPFS is declared as 38.5 months for the lanreotide arm in updated results (Wolin 2017, Caplin 2021). SSAs can be recommended for tumour growth control in advanced SSTR-positive (although SSTR status is not predictive of response), slowly-growing NETs up to a Ki-67 of 10%.

Everolimus: The registration trial (RADIANT-3 study) with 410 patients (including 40% therapy-naive patients) showed prolongation of PFS by 6.4 months in advanced progressive pNETs; median PFS was 11 months with everolimus and 4.6 months with placebo (Yao 2011). Everolimus is recommended in progressive pNET G1/G2 with or without prior chemotherapy. The efficacy of everolimus in advanced non-functioning gastrointestinal (GI) NETs with poor prognosis was evaluated in the RADIANT-4 trial, in which 302 patients with GI and lung NETs were included. Median PFS was 11 months with everolimus and 3.9 months with placebo [hazard ratio (HR) 0.48]. There was a benefit in terms of PFS prolongation in the GI subgroup [HR 0.56 (0.37, 0.8)] and the lung NET subgroup [HR 0.5 (0.28e0.88)] (Yao 2016).

Sunitinib is the only multitarget TKI that is EMA-approved in pNETs. In a randomised trial, sunitinib (37.5 mg/day) was compared with placebo in 171 patients with advanced unresectable pNETs. A significantly longer PFS (11.4 versus 5.5 months) was noticed in favour of sunitinib, while ORR was <10%; there was a trend toward an OS benefit with sunitinib (Faivre 2017).

Peptide receptor radionuclide therapy (PRRT) is a therapeutic option in progressive SSTR-positive NETs with homogenous SSTR expression (all NET lesions are positive) assessed by SSTR imaging. The two peptides most commonly used for PRRT are DOTATOC and DOTATATE. ^{177}Lu is increasingly preferred to yttrium-90 (90Y)-labelled SSA due to its much lower kidney toxicity and the possibility to carry out scintigraphy and thus dosimetry. The multicentre prospective phase III NETTER-1 trial has compared ^{177}Lu-DOTATATE in association with 30 mg octreotide versus 60 mg octreotide alone (every 4 weeks) in 229 patients with metastatic well-differentiated (G1/G2) midgut NETs. Patients had progressive disease within a time frame of up to 3 years, and all had previously been treated with a standard dose of SSA. ^{177}Lu-DOTATATE was superior to high-dose octreotide in terms of PFS (primary end point). Median PFS (mPFS) with ^{177}Lu-DOTATATE was 28.4 months while it was 8.5 months with high-dose octreotide (HR for disease progression 0.214; 95% CI 0.139e0.331). ^{177}Lu-DOTATATE was also associated with a higher ORR (18% versus 3%) at 3 months after the fourth PRRT cycle. OS analysis is premature and indicates a trend towards OS benefit (Strosberg 2017). ^{177}Lu-DOTATATE is EMA-approved for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), SSR-positive gastroenteropancreatic NETs.

About the product

Surufatinib is a small molecule, multikinase inhibitor, that potently inhibits vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3; fibroblast growth factor receptor-1 (FGFR-1); and colony-stimulating factor-1 receptor (CSF1R) with high specificity (50% inhibitory concentration of 1 to 24 nM).

Claimed indication: Sevsury is indicated for for use as monotherapy for the treatment of adult patients with low grade (grade 1 [G1] or intermediate grade (grade 2 [G2]) progressive neuroendocrine tumours of extrapancreatic or pancreatic origin that are unresectable locally advanced or metastatic.

Posology: The recommended dose of Sevsury is 300 mg once a day until disease progression or intolerable toxicity.

The development programme/compliance with guidance/scientific advice

To date, 15 clinical studies with surufatinib have been conducted (6 in healthy subjects and 9 in patients with cancer, of which 5 are ongoing). All clinical studies of surufatinib in patients with cancer, except for the ongoing phase 1/1b study in the United States (Study 2015 012 00US1), were conducted in China.

The current application is based on two pivotal phase 3 studies: SANET-ep, conducted in patients with NETs of extrapancreatic origin and SANET-p, in patients with pancreatic NETs. Two additional studies (studies 2015-012-00US1 in US patients and 2014 012 00CH1 in Chinese patients) provide supportive efficacy data.

Scientific Advice: The applicant received Scientific advice from the CHMP in June 2020, when both studies were already terminated. Regarding clinical development, the main question focused on extrapolation of data from the SANET-ep and SANET-p studies to the European population. The CHMP stated that the potential impact of any advice was limited because the clinical studies had already been conducted and preliminary results were available, emphasising that pre-assessment of these data was not the scope of the SAWP. Concerning extrapolation to the EU population, it was stated that B/R could be seriously hampered by the fact that both studies were conducted with placebo as comparator, when systemic treatment choices were available in EU. Another question on the potential need for additional ECG (QTc) data as a post-marketing commitment was deemed a post-submission review issue.

General comments on compliance with GMP, GLP, GCP

GMP: Please see further above

GLP: Some issues in relation to GLP has been discussed, please refer to the overall assessment

GCP: The applicant claims that all clinical studies included in the clinical development of surufatinib were conducted in accordance with standard operating procedures of the Sponsor and/or delegated contract research organization, which comply with the principles of Good Clinical Practice for the design, conduct, and analysis of the clinical studies. All studies were conducted under the approval of local ethics committees or institutional review boards. Before participation in the clinical studies, all subjects and patients provided informed consent. These studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the subject or patient. Where required, regulatory discussion with and approval from the appropriate health authority were obtained before study conduct.

Type of application and other comments on the submitted dossier

Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

PRIME

NA

Accelerated assessment

NA

Conditional marketing authorisation

NA

Marketing authorisation under exceptional circumstances

NA

Biosimilarity

NA

Additional data exclusivity/ marketing protection

NA

New active substance status

The applicant requested the active substance surufatinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Assessment of this claim is appended.

Orphan designation

NA

Similarity with orphan medicinal products

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

Derogation(s) from orphan market exclusivity

NA

Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0142/221 on the agreement of a paediatric investigation plan (PIP)

At the time of submission of the application, the PIP not yet completed as some measures were deferred.

Scientific overview and discussion

Quality aspects

Introduction

The finished product is presented as an immediate release hard capsule containing 50 mg of surufatinib as active substance.

Other ingredients are:

Capsule content: Microcrystalline cellulose, mannitol, sodium starch glycolate, povidone, magnesium stearate

Capsule shell: Gelatin, titanium dioxide (E171), allura red AC (E129), brilliant blue FCF (E133)

Printing ink: Shellac, propylene glycol, potassium hydroxide, black iron oxide (E172)

The product is available in blister packs sealed in a child-resistant Key-Pak® Plus wallet card in pack sizes of 168 capsules. The blister pack consists of polyvinyl chloride/polyethylene/ polyvinylidene chloride composite sheets, which are molded with cavities and hold the capsules, and a press-through-packing aluminum foil lidding (aluminum-plastic blister pack). The wallet is made of tear-resistant cardboard.

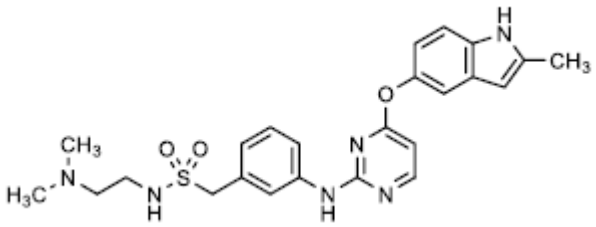
Active Substance

General Information

Information on the manufacture and control of the drug substance is submitted as full file.

The drug substance is small molecule named surufatinib (N-[2-(Dimethylamino)ethyl]-1-[3-({4-[(2-methyl-1H-indol-5-yl)oxy]pyrimidin-2-yl}amino)phenyl] methanesulfonamide). The INN is Surufatinib. The active substance is a non-chiral compound. The structural formula, the molecular formula as well as the relative molecular mass of Surufatinib are included in the dossier.

Structural formula (CTD section: S.1.2)



Surufatinib is a white to off-white powder. The manufacturing process yields a crystalline polymorphic form of surufatinib.

Solubility of surufatinib in aqueous media at different physiologically relevant pH values has been investigated. Surufatinib is soluble in acidic aqueous medium and solubility decreases significantly with increasing pH.

The particle size distribution is a specified parameter of the API specification, the aimed particle size distribution is described in S.1.3.

The section S.1 includes overview of relevant physicochemical properties.

Manufacture, process controls and characterisation

Manufacture

The name, site address and responsibility of each manufacturer involved in the manufacturing and testing is provided. Information provided is sufficient.

QP declaration

A QP declaration for EU GMP compliance is provided (EMA/334808/2014) and includes all relevant manufacturing sites of the active substance. The QP declaration is provided in the template.

Manufacturing process

The synthesis of surufatinib occurs in multiple chemical steps.

Schematic representations of the manufacture of the active substance Surufatinib are provided. A narrative description of the manufacturing process is included as well.

The manufacture of the key intermediate comprises three steps. The manufacture of the key intermediate is followed by the three-step manufacturing process of Surufatinib. The first step is a chemical transformation step. The second step in the manufacture of Surufatinib involves chemical transformation and crystallisation followed by recrystallisation. In the last step of the synthesis a micronisation step is performed. In total, a six-step manufacturing process has been established with 5 chemical transformation steps and one milling step.

The flow charts include chemical structures of the starting materials, intermediates and Surufatinib. However, the molecular formulae of starting materials, intermediates and the active substance are included. The type of chemical reactions are stated for each step in the synthesis. Reagents, solvents and the catalyst are stated as well. The non-isolated intermediate is depicted in squared brackets.

The narrative describes each step in the manufacturing process. The narrative description of the process has been revised to include additional details on reaction conditions (e.g. temperature ranges), operating conditions (e.g. speeds of stirring steps as well as centrifugation speeds and times) and equipment types.

Molecular weights and weight ratios for the used materials of each manufacturing step are listed. Input and output in kg for each step are clearly stated.

Information on the obtained batch size ranges for each step is provided.

Yields or yield ranges for each stage are provided in the narrative.

All in-process control used in the manufacture of Surufatinib along with their method descriptions and acceptance criteria are submitted.

Starting materials

Overall, the proposed starting materials have been properly justified. Synthetic schemes representing the synthesis of the proposed starting materials are presented in support of the proposed specifications. Potential impurities are discussed, and their fate down-stream investigated. Impurity specifications are supported by spike/purge studies. CoA are presented for each starting material representing used suppliers. Few points for clarification, raised regarding the proposed starting material specifications, have been satisfactorily resolved.

The following information is provided for each starting material: chemical name, molecular formulae, molecular weight, physical state as well as names and addresses of the respective manufacturers. Well defined starting materials with acceptable specifications are used.

Reagents, solvents and auxiliary materials

Specifications for all materials and solvents used in the preparation of Surufatinib are provided in 3.2.S.2.3. Specifications for materials and solvents used in the manufacture of a key intermediate have been submitted as well. Mandatory parameter identity (or appearance along with other specific parameters) is specified for all used materials. Test methods are informed.

The use of potable water in synthesis is acceptable as there is no requirement for sterility or apryrogenicity in API in which it will be used (API will be used for an oral preparation – non-sterile medicinal product). This is in-line with EMA/CHMP/CVMP/QWP/496873/2018. A specification for 'water' used in the manufacture of the key intermediate is provided. It has been confirmed that the quality of this water is in-line with potable water as described in EMA/CHMP/CVMP/QWP/496873/2018.

The drug substance manufacturer provided a specification for 'purified water'. This type of water is used in the drug substance synthesis.

No class 1 solvents are used. However, benzene may arise from another solvent, where benzene is a known process impurity. Appropriate limits for benzene are included in specifications for relevant solvents.

Material of human or animal origin

In section 3.2.S.2.3 it is stated that all materials used to manufacture the drug substance are without risk of transmitting agents of animal spongiform encephalopathies.

Control of critical steps

Tests and acceptance criteria performed at critical steps, identified in 3.2.S.2.2 of the manufacturing process, have been described, and justified based on experimental data.

Intermediates

For the non-isolated intermediate, an in-process control to test for completeness of reaction is described in 3.2.S.2.2 and this is appropriate.

Quality and control of isolated intermediates are described in dossier section 3.2.S.2.4. The isolated intermediates are characterized, and their quality controlled during the manufacture of surufatinib.

Appropriate specifications are established for each isolated intermediate. Analytical methods are described in the dossier. Few points for clarification, raised recommending establishment of limits for total impurities and tightening of limits for potential impurities with reference to available batch data, have been satisfactorily resolved.

Intermediate: a specification with parameters appearance, ID by HPLC, water content, purity, related substances as well as assay are included, and this is appropriate. Batch data has been presented and all specification limits are met.

Potential impurities are presented, and their fate down-stream elaborated. Specifications for potential impurities are established based on spike/purge studies, which demonstrated the process capability to purge the respective impurities.

Key intermediate: a specification with parameters appearance, ID by HPLC-UV, water content, residual catalyst, purity, related substances, residual solvent and assay are included, and this is appropriate. Batch data has been presented and all specification limits are met. Potential impurities are presented, and their fate down-stream elaborated. Specifications for potential impurities are established based on spike/purge studies, which demonstrated the process capability to purge the respective impurities. The

specification has been updated to include a limit for total impurities. In addition, acceptance criteria for the specified impurities have been tightened based on the batch data.

Intermediate: a specification with parameters appearance, ID by NMR, ID by MS, ID by HPLC, purity, related substances as well as assay are included, and this is appropriate. Batch data has been presented and all specification limits are met. Potential impurities are presented, and their fate down-stream elaborated. Specifications for potential impurities are established based on spike/purge studies, which demonstrated the process capability to purge the respective impurities. A question is raised regarding missing limit for total impurities. The specification has been updated to include a limit for total impurities.

Intermediate: a specification with parameters purity and related substances is provided. Parameter identity is not included in the specification, but ID is tested in a subsequent intermediate. Batch data has been presented. Potential impurities are presented, and their fate down-stream elaborated. Specifications for potential impurities are established based on spike/purge studies, which demonstrated the process capability to purge the respective impurities. The specification has been updated to include a limit for total impurities and a limit for any other single impurity.

Intermediate: a specification with parameters purity and related substances is provided. Parameter identity is not included in the specification, but ID is tested in the subsequent intermediate. Batch data has been presented. Potential impurities are presented, and their fate down-stream elaborated. Specifications for potential impurities are established based on spike/purge studies, which demonstrated the process capability to purge the respective impurities. The specification has been updated to include a limit for total impurities.

Intermediate: a specification with parameters appearance, ID by HPLC, ID by IR, polymorphic form, water content, related substances, residual solvents, residue on ignition, residual catalyst and assay is provided. The limit for any other singly impurity is set in line with the identification threshold according to ICH Q3A. The acceptance criteria for residual solvents are in line with ICH Q3C.

Process validation

It has been confirmed that the proposed manufacturing process has been validated.

Manufacturing process development

Quality by design elements are used during the manufacturing process development.

The evolution of commercial manufacturing process is described. It is stated that the synthetic route has remained the same throughout development from early toxicological studies to late stage clinical studies. It is explained that a few process and operational modifications have been made. The major modifications are highlighted in the dossier.

The applicant has discussed in detail all manufacturing steps, process parameters and controls thereof. A summary of the process risk assessment for the manufacture of Surufatinib is included in the dossier. The CPPs and non-CPPs were identified for the manufacturing process and proven acceptable ranges (PARs) and Normal operating ranges (NORs) were established, for all process parameters for each operation, in order to assure consistent quality of Surufatinib.

Particle size distribution is included in the specification of Surufatinib. The (critical) quality attributes and overall control strategy are summarized in the dossier. The provided information is considered sufficient.

In section 3.2.S.2.6.4 the formation and control of related substances is discussed.

The fate and purge of potential impurities in the starting materials and intermediates have been studied and corresponding data of spiking experiments have been submitted.

Characterisation

The structure of surufatinib is confirmed from spectral analysis including infrared, ultraviolet-visible, nuclear magnetic resonance (1H NMR, 13C NMR, 13C NMR DEPT, 1H-1H COSY NMR, HMBC NMR and HMQC NMR), mass spectrometry and a single crystal X-ray diffraction study. The used methods are considered suitable. Respective spectra and results are provided in the dossier.

The physicochemical characteristics of the surufatinib including appearance, thermal analysis, hygroscopicity, solubility, dissociation constant, partition coefficient and particle size distribution have been determined using representative batches of surufatinib.

X-ray powder diffractometer, DSC and TGA were used for analysis of polymorphic forms generated during a polymorph screening. Respective data and powder X-Ray diffraction patterns are provided. Particle size distribution and the polymorphic form of the active substance are controlled parameters in the specification of Surufatinib.

Impurities

The impurity profile of surufatinib has been satisfactorily explored investigating fate and the process purge factor for potential impurities originating from the starting materials, potential side products and degradation products.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specification/ analytical procedures

The drug substance specification includes appropriate test parameters, including appearance, identification by IR, identification by HPLC, polymorphic form by XRDP, related substance by HPLC, residual solvents by GC, water content by KF, residue on ignition, particle size distribution by laser light distribution and assay by HPLC. In-house methods are used for most of the tests. Where applicable, reference to Ph. Eur. is made. All methods referenced in the specification of surufatinib are sufficiently described. The applied analytical methods have been satisfactorily validated in line with the current guideline.

Related substances method: LOD and LOQ for surufatinib and the specified process impurities are determined (0.02% and 0.05%, respectively). The method was shown to be stability indicating. All validation and verification results met the requirements, indicating that the methods are accurate, reliable, and suitable for testing of surufatinib.

The maximum daily dose of surufatinib of 300 mg is used to establish specification limits for related substances.

The specified limits for the process impurities are below the qualified levels from non-clinical toxicological safety studies on a toxicological batch. Upon request, the acceptance criteria for specified impurities and total impurities have been further tightened based on the batch data for the most recent batches to guarantee a consistent quality. In the same manner, the specifications for particle size distribution, water content and assay have been tightened based on the batch data. The updated drug substance specification is acceptable.

The proposed strategy for control of residual solvents in the drug substance has been satisfactorily justified.

Genotoxic impurity evaluation has been performed following principals of ICH M7. Two complementary predictive methodologies, one rules-based and one statistical based, were utilized to determine whether or not each reaction component or potential impurity was of mutagenic concern. Derek was used as the rules-based methodology. Sarah was used as the statistical-based methodology.

The risk assessment for potential formation of nitrosamine impurities during the manufacture and storage of the surufatinib drug substance has been performed in line with the current regulatory expectations. Since no nitrite salts or other nitrosating agents are used in any steps of the synthesis of surufatinib, the risk of the amines to convert to N-nitrosamines is low. Process water has been considered as potential source of nitrite. The risk of introducing nitrosamines from the packaging materials for drug substance, intermediates, and starting materials is also very low. Overall, no risk of formation of nitrosamines during synthesis of the drug substance has been identified.

The risk assessment for elemental impurities has been performed according to ICH Q3D. Omission of testing of other elemental impurities has been satisfactorily justified.

Batch analysis

Batch analysis data are presented for all historical batches and illustrate qualities of the drug substance used during the clinical phases.

Batch analysis are provided for the batch used in the bioavailability study, 3 batches used in the primary stability study and 3 batches used in process validation and supporting validation studies. Results comply with specifications.

The manufacturing process has been optimized over time, however no CoA are presented for the proposed process. Upon request, the Applicant has presented CoA for three drug substance batches manufactured according to the commercial process.

Container closure

Surufatinib is packaged into low-density polyethylene bags. This bag is then placed in an outer laminated bag, which is heat sealed. The primary packaging complies with Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food. The primary packaging complies with the Ph. Eur. 3.13. The specification for the primary packaging, LDPE bag, includes Identification test by IR. The proposed container closure system is used in the stability studies and it provides proper protection.

Stability

The re-test period/ storage conditions is proposed for the drug substance stored in the proposed container closure system (LDPE bag placed in an aluminium foil bag). The requested re-test period and storage conditions are based on long-term, intermediate and accelerated data obtained.

The investigated stability batches were manufactured according to two processes, which are slightly different from the commercial manufacturing process. It has been discussed whether or not last changes to the process, could have an impact on stability of the drug substance. It is argued that the minor differences have no impact on the drug substance quality as well as the quality of the intermediates. The data analysis are provided in 3.2.S.2.4 *Controls of Critical Steps and Intermediates* and the results show that the quality of these batches is equivalent.

Comparing the quality of batches obtained from different processes, it can be concluded that the drug substance manufactured are representative to the one from commercial process, and the proposed re-test period is representative to that of the commercial product.

The proposed re-test period can be accepted for the drug substance in the sealed container closure system. Photostability study of the drug substance has been investigated in line with the current guideline on Photostability Testing of New Active Substances and Medicinal Products (ICH Topic Q1B). The active substance is not sensitive to light.

Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is immediate release hard capsules, to be marketed in blister packs sealed in a child-resistant Key-Pak® Plus wallet card in pack sizes of 168 capsules. The blister pack consists of polyvinyl chloride/polyethylene/ polyvinylidene chloride composite sheets, which are molded with cavities and hold the capsules, and a press-through-packing aluminium foil lidding (aluminium-plastic blister pack). The wallet is made of tear-resistant cardboard.

The finished product is described as off-white powder filled into a size 3 hard gelatin capsule with Swedish orange opaque cap and white opaque body, imprinted with "50mg" on the body in black ink.The recommended dose of Sevsury is 300 mg (i.e. six 50 mg capsules) once a day until disease progression or intolerable toxicity. Dose can be adjusted to manage adverse reactions, dose is reduced in 50 mg intervals.

The description and composition of the finished product is considered acceptable, including information on the size of the finished product in mm, reference to Ph. Eur. For relevant excipients, confirmation of compliance with (EU)231/2012 for colourants and compendial names for all excipients.

Pharmaceutical development:

Relevant physico-chemical properties of the active substance have been addressed. Particle size was considered to have influence on drug product critical attributes, e.g. dissolution. Solubility is pH dependent.

Compatibility with regard to excipients has been demonstrated as well as justified by stability data. There is no API overage in the formulation. The choice and function of the excipients in the formulation has been described in general terms. However, functionality related characteristics of the excipients have not been addressed. Discussion on the grades of excipients including defining appropriate acceptance criteria for functionality related characteristics are required.

Finished product pharmaceutical development and control strategy are considered traditional.

Formulation development has been sufficiently described. Active substance particle size was investigated and found to influence on dissolution. Reduction in particle size by micronization showed positive effects on dissolution leading to a particle size range, which was finally established as the release criteria for the active substance.

The development of the dissolution test method has been appropriately addressed and discriminatory properties of the method demonstrated, with regard to particle size of the active substance and amount of binder. The chosen dissolution method and acceptance criteria are considered acceptable.

The choice of high-shear wet granulation for the manufacture of the capsule content has been justified. Critical process parameters were identified. Based on analysis of the drying parameters and LOD data of all the batches of granules, the acceptable drying process parameters were determined.

The process is verified by data on three consecutive batches manufactured at the commercial scale using the proposed manufacturing conditions and in-process controls and additional sampling.

The choice the packaging material have been appropriately addressed and is considered suitable. A risk assessment has been performed regarding the potential impact of the CRP operation on the drug product. Stability data presented under P.8.3 Stability Data, were carried out with carton as secondary packaging. The risk assessment is considered acceptable, and supported by three months stability data on two commercial scale batches of the finished product packed in the commercial secondary packaging

Manufacture of the product and process controls

Manufacture

Name, address and responsibility of each site involved in the manufacturing and testing of the finished product intermediate and the finished product have been given.

Until a valid GMP certificate issued by a European authority can be presented, this is kept as a major objection.

The manufacturing process and dosage form are considered standard. The finished product is a wet granulation of surufatinib drug substance with commonly used excipients that is filled in a hard gelatin capsule.

Overall, the manufacturing process is considered described in sufficient details, including relevant process parameters and operating ranges. The set points and ranges has been justified by pharmaceutical development and confirmed by process evaluation data.

Process controls

The critical steps and in-process controls identified, are considered to reduce the risks identified during formulation and process development and is considered acceptable for this standard process.

The process is considered as a standard process.

Excipients

Most excipients used for capsule content comply with the requirements of their respective current Ph. Eur. monographs. Appropriate, specifications for the critical functionality-related characteristics should be set and included in the specifications for relevant excipients. For the capsule shell a justified specification is provided including relevant parameters and limits. Titanium dioxide and other colouring agents comply to (EU)231/2012.

Gelatine, which is used in the manufacture of the capsule shell is of bovine origin. Respective CEPs and compliance statements are provided in section 3.2.R. The manufacturers are mentioned on a TSE/BSE statement. Magnesium stearate is of vegetable origin. Therefore, no risk of BSE is anticipated.

Specifications

Overall, the finished product release and shelf-life specifications (see table below) have been adequately set in accordance with EU/ICH Q6A, Ph. Eur. and is recognised to be based on comprehensive batch and stability data available. Specifications include appearance (visual inspection), identification by HPLC, identification by UV (Ph. Eur. 2.2.25), related substances (specified, single, and total impurities) by HPLC, uniformity of mass (Ph. Eur. 2.9.5), dissolution (Ph. Eur. 2.9.3), water content (Ph. Eur. 2.5.12) and microbial limits (Ph. Eur. 2.6.12 and 2.6.13). The release and shelf-life specification has been updated to include the same tests, and specification limits are considered justified.

Ph. Eur. methods are used for determination of microbiological purity as well as relevant chapters are applied with regard to uniformity of dosage units (CU), dissolution and water content. Otherwise, in-house methods are used. Descriptions of the in-house analytical methods have been presented.

The in-house methods have been described in detail including the principle of the method, the equipment parameters, the sample and standard preparation, the calculation formula, and a system suitability test. The applied methods are in accordance with current technical and scientific requirements.

Different HPLC methods are used for assay and related substances. The methods have been satisfactorily validated in accordance with ICH Q2 and are considered adequate to control the finished product on a routine basis.

Batch analysis

Extensive batch data has been presented. The results confirm the consistency and uniformity of the drug product and robustness of the manufacturing process. Batch analysis data include data on representative batches manufactured with the commercial capsule shell.

Process related impurities and degradation products including potential degradation pathways and theoretical degradation products, forced degradation studies and stability studies have been appropriately discussed. Two process related impurities are specified in the finished product specification due to their levels and with consideration that stability data on capsules packaged in blister packs is limited, which is considered acceptable. Other theoretical degradation products are controlled as non-specified impurities, which is acceptable. An acceptable risk assessment for elemental impurities has been provided (including test results of stability batches).

The nitrosamine risk assessment addresses the drug substance, all excipients including water and packaging material. It is concluded that there is low risk of introducing nitrosamine impurity during the manufacturing of surufatinib capsules. A theoretical calculation of the maximal percentage of potential nitrosamines per unit dose is presented based on maximum levels of nitrites and nitrates in each excipient. The proposed acceptable limit for nitrosamines in surufatinib according to ICH Q3B is agreed, as the product is intended for treatment of advanced cancer in the scope of ICH S9 guideline. Considering the acceptable limit, further testing on the finished product is not further pursued, and the theoretical calculation accepted. Limits for parameters included in the specification are justified including assay, specified impurities, total impurities and water. Dissolution.

Reference Standards or Materials

The reference standard batches used for qualitative and quantitative analysis of surufatinib capsules are the same as those used for the drug substance.

Container Closure System

The presented information on the container closure system is considered acceptable, and the choice of container closure system is justified. The provided information on primary packaging covers description, specifications (including IR), drawings and lists the used manufacturers. A declaration on compliance of the manufacturers (e.g. 10/2011 and Ph. Eur. 3.1.11 and 3.1.3) has been included. Same primary packaging has been used for stability studies. Three months stability data is presented for two commercial scale batches packed in the secondary container closure system proposed for marketing.

Stability of the product

The presented stability studies on primary stability batches has been carried out in accordance with current ICH guidelines.

Except for the sampling time point of the dissolution method and the dilution of sample solution for total yeasts and moulds count (TYMC) and the bacterial strains used for the method validation of the microbial limits test method, the methods used in the stability testing of the primary and supporting stability batches were consistent with the methods referenced in the specification for surufatinib capsules, and there was no change during the study.

The proposed shelf-life is considered acceptable. As there is no or little change over time and only variability for assay, it is considered acceptable to extrapolate shelf-life to 24 months based on 18 months stability data.

All presented stability data under long-term and accelerated conditions comply with proposed specifications. No storage condition with regard to temperature is specified for the finished product, and considered acceptable.

A sufficiently detailed post-approval stability protocol has been provided. Ongoing stability studies will also be continued.

Stress testing (60°C, 75%RH and light) revealed no significant change of unpacked or packed capsules. 90% RH showed negative effects (about 12% weight gain), when product was unpacked. Data demonstrate adequate protection of the capsules, when suitable packaging was chosen.

Stress testing includes a photostability study with light exposure according to ICH requirements (Q1B, Option 2). Results demonstrate that no significant changes in any of the tested parameter were observed after light exposure for either unpacked capsules, capsules in blister packs or blister packs in carton. No storage condition with regard to light is required.

Stability studies have been conducted on 3 commercial batches in line with EU/ICH guidance with finished product batches in proposed commercial primary packaging material. Stability data at accelerated conditions for up to 6 months (40°C/75%RH), long-term (25°C/60%RH, 18 months) and intermediate (30°C/65%RH, 12 months) conditions are included in the section. Results show no negative trends in any of the tested parameters.

The secondary packaging material applied for stability studies is carton. The proposed commercial secondary packaging material is Keystone Key-Pak® Plus wallets. The Applicant has presented a risk assessment concluding that the proposed CRP operation presents a low risk to drug product quality and stability. 3 months stability data on the finished product packaged in the commercial container closure system (i.e., blister packs sealed in the secondary Keystone Key-Pak® Plus wallets) on two batches is available and confirm that the proposed CRP operation does not influence on stability of the finished product.

Post approval change management protocol(s)

Not applicable.

Adventitious agents

Not applicable.

GMO

Not applicable.

Discussion and conclusions on chemical, pharmaceutical and biological aspects

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Sevsury, 50 mg, hard capsules are of sufficient quality in view of the present European regulatory requirements, however a recommendation for marketing authorisation cannot be given until a valid GMP certificate is available. In addition, few points for clarification remain to be resolved.

Non-clinical aspects

Introduction

The sought indication is treatment of adult patients with low or intermediate grade (grade 1 (G1) or grade 2 (G2) progressive neuroendocrine tumours of extrapancreatic or pancreatic origin that are locally advanced or metastatic which falls within the scope of ICH guideline S9, hence a non-clinical study program in line with ICH S9 has been performed.

Per CHMP scientific advice a selected set of non-clinical studies were repeated under OECD and/or US FDA GLP regulations. Among these, 13-week repeat-dose toxicity studies in rats and dogs were conducted at Covance Pharmaceutical R&D in Shanghai (China), phototoxicity study in guinea pigs at Innostar, Shanghai (China) and the hERG assay at WuXi AppTec, Suzhou (China). The Applicant concludes that although these test facilities are not within a mutual acceptance of data (MAD) country, the sites have been audited for OECD GLP compliance by the Belgian and Dutch health authorities, respectively, in a time period relevant to the conduct of the studies.

Covance, Shanghai was fully inspected including study audits by Belgian authorities in 2018. The next inspection in 2020 was - due to coronavirus pandemic - a remote inspection without study audits and facility visit. WuXi AppTec, Suzhou was inspected by Belgium in 2018 including facility visit and study audit. The next inspection was performed by Belgian authorities in January 2020, however the nature of inspection was not informed. Innostar Biotech, Shanghai was fully inspected by Dutch authority in 2019.
All above-mentioned non-clinical studies for surufatinib at three Chinese test facilities were completed in 2020. Hence, presumably no dedicated full inspection has been performed on any above mentioned non-clinical study of surufatinib by any European authority. However, based on the fact that GLP inspections are harmonized across all OECD MAD countries GLP site inspection conducted by the Belgian and Dutch GLP Compliance monitoring Authorities at Wuxi AppTec, Covance and Innostar could be accepted in the context of the assessment of surufatinib provided there are no concerns on the data or on the inspection results. There are currently no special concerns regarding the quality of the above-mentioned nonclinical studies except that TK in pivotal rat and dog studies used bioanalytical methods that were not validated in compliance with OECD GLP. However, it appears that the intended Belgian GLP Monitoring program including full inspections every two years is not completely fulfilled at Wuxi AppTec Suzhou and Covance Shanghai. To avoid triggering study inspection and to ensure OECD GLP-compliance the Sponsor was asked to submit the inspection reports of these Chinese test facilities issued by Netherlands and Belgium covering the time of conduct of these non-clinical studies of surufatinib.

The requested inspection reports were subsequently made available for assessment; however, some other concerns remain to be clarified:

- Regarding Final inspection report (2018) issued by Sciensano, Belgium, date of inspection in Covance, Shanghai is 19-21 March 2018. However, on page 8 of the report it is stated that the inspection was third full inspection, 19-22 January 2016. Moreover, in the footnote the report is named as "GLP inspection report 2016 Covance".
- In inspection reports, the audited non-clinical studies have been hidden, thus it is not known if any of the surufatinib studies were audited.
- Regarding the remotely conducted GLP inspection at Covance Shanghai in July 2020, the inspection was claimed to be a full inspection of the Test Facility. This is not agreed, since the inspection covered the general Quality management, but study audits, which are in scope of full GLP inspection were excluded.

Pharmacology

Primary pharmacodynamic studies

Surufatinib is a small molecule antitumor drug for the treatment of locally advanced or metastatic neuroendocrine tumors of pancreatic or extra-pancreatic origin. Surufatinib selectively inhibits vascular endothelial growth factor receptors 1, 2, and 3, the fibroblast growth factor receptor 1 and the colony-stimulating factor 1 receptor tyrosine kinases thereby effectively inhibiting tumor angiogenesis.

The role of surufatinib as a tumor immunomodulator was briefly described with reference to the literature in the non-clinical and pharmacology overviews. However, as no studies were presented in that regard this mode of action was not assessed.

Five in vitro pharmacology studies were conducted to determine the binding characteristics, functional activity and anti-angiogenic effects of surufatinib. Surufatinib had potent inhibitory activity on the VEGFR2 kinase with an IC50 = 17 ± 6 nM (study No 2014-012-01). Surufatinib inhibited VEGFR1, VEGFR2, VEGFR3, CSF1R, and FGFR1 with IC50s < 0.025 μM in a selectivity study over multiple kinases (study No 2014-012-02). Out of a panel of 223 kinases surufatinib selectively and potently (> 95%) inhibited the following 11 of 223 kinases: Abl proto-oncogene (Abl)Q252H, AblY253F, AblH396P, Met proto-oncogene (Met)D1246N, MetY1248D, MetY1248C, MetM1268T, FGFR2N549H, platelet-derived growth factor receptor (PDGFR)-αV561D, c-Kit proto-oncogene (c-Kit)V560G, and feline McDonough sarcoma (FMS)Y969C (study No 2014-012-08).

Surufatinib potently inhibited VEGF-induced VEGFR2 phosphorylation in HEK-293 cells with an IC50 of 2 ±1 nM. Surufatinib also simultaneously inhibited the activation of VEGFR2 downstream signalling molecules, including protein kinase B (AKT), Src, and extracellular signal-related kinase 1/2 (ERK1/2) in both primary human umbilical vein endothelial cells (HUVECs) and HEK-293-VEGFR2 cells. Surufatinib inhibited VEGF-dependent HUVEC proliferation with an IC50 of 16 ± 7 nM. The tubular branching of primary HUVECs was inhibited by surufatinib by 75% at 0.3 μM without obvious cytotoxicity (study No 2014-012-03).

At the isolated organ tissue level, surufatinib also had an inhibitory effect on microvessel formation in rat aortic rings rings in a dose-dependent manner with an IC50 of 192 nM (study No 2014-012-04). It should be noted that the IC50 of 192 nM is approximately 5-fold greater than the unbound human steady-state Cmax for the proposed clinical dose of 300 mg/day surufatinib from study No 2015 012-00US1 (18.7 ng/mL based on a total Cmax of 456 ng/mL and a protein binding of 95.9%).

Surufatinib exerted strong inhibitory activity on kinases of the VEGFR family and blocked the activation of intracellular VEGFR2 and its downstream signalling pathways. In addition, surufatinib inhibited microvessel formation in a concentration-dependent manner in the rat aortic ring model. Therefore, in vitro proof of concept and mechanism of action of surufatinib were established and is supported.

Three studies evaluated the in vivo pharmacological activity of surufatinib in BALB/c nude mice as the relevant species. The on-target activity of surufatinib was confirmed in nude mice given a single oral dose up to 80 mg/kg. Surufatinib-treatment resulted in dose- and time-dependent inhibition of VEGF-induced VEGFR2 phosphorylation in lung tissue from mice. Oral doses at 20 and 40 mg/kg completely inhibited VEGF-stimulated VEGFR2 phosphorylation for 4 hours post dose (corresponding to a plasma drug concentration > 181 ng/mL 4 hours after 20-mg/kg dose). At 80 mg/kg, surufatinib depressed VEGFR2 phosphorylation by over 100% for 8 hours (study No 2014-012-07).

Surufatinib demonstrated high potency and dose-dependently inhibited tumor growth in multiple human tumor xenografts including human gastric cancer BGC-823, non-small-cell lung carcinoma NCIH460, metastatic renal cell carcinoma Caki-1, and colon cancer HT-29 in BALB/c nude mice orally dosed at 20 to 80 mg/kg/dose twice daily. Among the four models, gastric cancer BGC-823 showed the highest sensitivity to surufatinib (study No 2014-012-05).

The anti-angiogenesis effect of surufatinib in the antitumor efficacy studies was investigated by detecting the changes of endothelial cell marker CD31 (PECAM-1) in the tumor tissue by immunohistochemistry technology. Surufatinib treatment at 20, 40, or 80 mg/kg/dose twice daily resulted in a dose-dependent inhibition of CD31-positive vascular area in tumors (47, 40, and 71% (NSCLC cells NCI-H460) and 32, 65, and 71% (RCC Caki-1), respectively) (study No 2014-012-06).

In vivo surufatinib inhibited phosphorylation of VEGFR2 in lung tissues in a time- and dose-dependent manner and activity on the growth of multiple tumor types in the nude mouse model. Thus, proof of concept and mode of action were demonstrated for surufatinib in the in vivo pharmacology studies. However, no justification for species selection in the in vivo studies was provided.

The dates and signatures for authentication are missing on study report Nos 2014-012-03, 2014-012-04, 2014-012-05 and 2014-012-07 and should be provided. In report Nos 2014-012-01, 2014-012-06 and 2014-012-08 date of version/report date (Sep-30-2014, Jan-15-2015 and Aug-30-2020, respectively) do not match with the date/year of signatures (2021). The Applicant is asked to explain these discrepancies.

Secondary pharmacodynamic studies

The potential off-target secondary pharmacodynamic activity of surufatinib was evaluated in vitro using selectivity assays against a panel of 87 enzymes, receptors and ion channels. Surufatinib at 3 μM demonstrated significant binding or inhibition on 11 targets (study No 100053308). The effects on central nervous system-related receptors (ie, kappa opioid, 5-HT2A, 5-HT2B, and 5-HT2C) were considered of minor importance due to limited distribution of surufatinib to the brain based on the results of the tissue distribution study in rats (study No 14763). When compared with the anticipated unbound maximum plasma concentration (Cmax) exposure (0.039 μM) in patients treated with surufatinib at 300 mg daily, the concentration associated with significant findings in the binding assay exceeded the clinical exposure by approximately 77-fold.

Safety pharmacology

Single oral administration of surufatinib up to 400 mg/kg, the highest dose employed, induced no adverse effects on motor activity, behaviour and coordination in ICR mice (study No 0830PB1).

In vitro, surufatinib inhibited hERG currents with an IC50 of 1.8 μM in a GLP study (study No 215-0075-EP) which is 46-fold above the clinical Cmax (free) at a dose of 300 mg (study No 2015-012-00US1) indicating a low risk for QTc prolongation. In addition, the non-GLP in vitro study Nos CRO090216-02 and CRO090314-02 demonstrated that surufatinib inhibited the hERG tail currents with

an IC50 of 4.9 ± 2.1 μM and 6.8 ± 0.7 μM, respectively. The compound mentioned as hERG-09-K2 in study No CRO090314-02 could not be identified as surufatinib.

In anaesthetized Beagle dogs, surufatinib following single oral gavage administration at a dose up to 60 mg/kg did not produce any treatment-related adverse effects on respiratory and cardiovascular system (study No 0830PH1). The study was conducted in anaesthetised animals and as stated in ICH guideline S7A "*…it is preferable to use unanesthetized animals. Data from unrestrained animals that may be chronically instrumented for telemetry, other suitable instrumentation methods for conscious animals, or animals conditioned to the laboratory environment are preferable to data from restrained or unconditioned animals*". Prior to recording respiratory and cardiovascular endpoints animals were anaesthetised in sodium pentobarbital, instrumented and inserted with catheters. Anaesthesia or surgery without sufficient analgesia is well known to cause profound effects on the respiratory and cardiovascular system. It was also noted that the only respiratory endpoint was the respiratory rate. Thus, the scientific contribution of this study appears limited.

In a GLP repeat-dose study in conscious Beagle dogs, surufatinib administered once daily via oral capsules at doses up to 12 mg/kg had no effects on quantitative or qualitative electrocardiogram parameters, including no QTc wave prolongation (study No 8422349).

The safety pharmacology assessment of surufatinib was carried out in accordance with the ICH guidelines S7A and S7B. In vitro and in vivo safety pharmacology studies evaluating the effects of surufatinib on the central nervous, respiratory and cardiovascular systems in mice and dogs were conducted in compliance with GLP. However, study Nos 0830PB1, 0830PH1, CRO090216-02 and CRO090314-02 were conducted under China's National Medical Products Administration GLP standards and do not fulfil the OECD principles of GLP. Furthermore, study Nos 8422349 and 215-0075-EP were not conducted within a mutual acceptance of data country but the test facilities were audited for OECD GLP compliance by the Belgian health authorities in a time period relevant to the conduct of the studies.

After the initial assessment of the above studies, the following non-clinical safety studies conducted under OECD GLP regulations were finalized and submitted for assessment by the Applicant:

CNS pharmacology study in rats (single-dose up to 120 mg/kg), study No 8459966.
Respiratory study in rats (single-dose up to 120 mg/kg), study No 8459960.
Cardiovascular study in conscious dogs (single-dose up to 60 mg/kg), study No 8459967.

In GLP study No 8459966 the neurological function was assessed by Modified Irwin Testing in female Sprague-Dawley rats administered a single oral gavage dose of surufatinib at doses up 120 mg/kg. No treatment-related effects were noted up to 24 hours postdose for any component of the modified Irwin battery of assessments.

In GLP study No 8459960 the respiratory function was assessed by plethysmography in female Sprague-Dawley rats administered a single oral gavage dose of surufatinib at doses up 120 mg/kg. No treatment-related effect was observed on tidal volume, respiration rate, or minute volume through 24 hours postdose.

In GLP study No 8459967 the cardiovascular function was assessed by telemetry in male Beagle dogs administered a single dose (via capsule) of surufatinib at doses up to 60 mg/kg. Administration of 12, 30, or 60 mg/kg caused increases in diastolic pressure by up to 12 mmHg (+16%) and mean arterial pressure by up to 11 mmHg (+11%). Administration of 30 or 60 mg/kg caused a decrease in arterial pulse pressure by 6 mmHg (up to -9%). No qualitative ECG abnormalities were noted, and no quantitative changes in PR interval, QRS duration, QT/QTc intervals, heart rate, systolic pressure, physical activity, or body temperature were attributed to surufatinib.

Based on the three GLP safety pharmacology studies, no effects on the respiratory or central nervous systems of rats were observed at doses up to 120 mg/kg. No clinically relevant changes in cardiovascular function in dogs were observed up to the maximum dose of 60 mg/kg. However, in study No 8459967 the Applicant should comment on the treatment-related changes seen in diastolic, mean arterial and arterial pulse pressure. In addition, as study No 8459967 claimed GLP the Applicant is asked to comment on the lack of GLP compliance for the bioanalytical, pharmacokinetic, electrocardiographic and statistical analytical phase reports.

Pharmacodynamic drug interactions

The omission of pharmacodynamic drug interaction studies is accepted as there are no drugs anticipated to be co-administered with surufatinib where a pharmacodynamic interaction is likely to occur.

Pharmacokinetics

Pharmacokinetics of surufatinib was studied in four in vivo studies in Sprague-Dawley rats and Beagle dogs after single i.v. or oral (oral gavage or capsules) administration (study Nos P-HMPL-012-ADME-1_RPK, RP-HMPL-012-ADME-1_DPK1, RP-HMPL-012-ADME-1_DPK1, DMPKR20120011-04 and XBLC14679N).

The toxicokinetics of surufatinib in rat and Beagle dog after repeated administration were assessed from two pivotal toxicology studies (study Nos 8422351 and 8422349) carried out in accordance with GLP consistent with the ICH guideline S3A. The rat and Beagle dog, were selected as the relevant test species in the pivotal toxicology studies.

Methods of analysis

The pharmacokinetics of surufatinib were evaluated in relevant animal species including rats, dogs, rabbits and guinea pigs.

The LC-MS/MS assay for the determination of surufatinib in sodium heparinized plasma from rat and dog was validated in terms of accuracy, precision, linearity, sensitivity (LLOQ), robustness, specificity and selectivity within the range 0.700 to 2800 ng/mL in a NMPA GLP study (study No RP-HMPL-012-ADME_Bioanalysis-MV). It was noted in the study that the Study Director's statement was signed by Analyst 2 and that the Study Director was also designated as Principal Investigator.
A LC-MS/MS method for quantitation of surufatinib in plasma from rat was validated and based on the results, it was determined that the reliability of the method for measuring the concentration of surufatinib in rat plasma was confirmed in the range 1.00 to 2000 ng/mL in a non-GLP study (study No A201014-T011-01). The dates and signatures for authentication were missing in the report.
A LC-MS/MS method for the determination of surufatinib in plasma from rat and rabbit was validated with regard to calibration, specificity, accuracy precision matrix effect and stability in the range of 1.00 to 2000 ng/mL in a non-GLP study (study No A201014-T011/T032/T034). The dates and signatures for authentication were missing in the report. It was difficult to gain an overview as the report only provided data.
A LC-MS/MS method for the determination of surufatinib in plasma from dog was validated with regard to specificity, sensitivity, accuracy, precision, matrix effect and stability in the range of 1.00 to 2000 ng/mL in a non-GLP study (study No 1.00 to 2000 ng/mL). The dates and signatures for authentication were missing in the report.
An LC-MS/MS method for the assessment of surufatinib in plasma from dog was validated with regard to precision, accuracy, calibration, specificity, matrix effect and stability in the range of 1.00 to 2000 ng/mL in a non-GLP study (study No A201014-T012/1038-001). The dates and signatures for

authentication were missing in the report. It was difficult to gain an overview as the report only provided data.
The LC-MS/MS method for quantitation of surufatinib sodium heparinized plasma from guinea pig was validated with regard to selectivity, carry-over, sensitivity, calibration, accuracy, precision, dilution integrity, matrix effect and stability in the range of 5.00 to 5000 ng/mL in a NMPA-GLP study (study No 19186MV04).

LC-MS/MS methods for quantitation of surufatinib in sodium heparinized plasma from rat and dog was adequately validated with regard to selectivity, carry-over, sensitivity, calibration, accuracy, precision, dilution integrity, matrix effect and stability in the range of 1.00 to 2000 ng/mL and 1.00 to 1000 ng/mL, respectively in non-GLP studies (study Nos 8422-345 and 8422-346). The bioanalytical methods (study Nos 8422-345 and 8422-346) validated to support the bioanalysis in the pivotal toxicology studies in dogs and rats (study Nos 8422349 and 8422351) and the embryo-fetal development study in rats (study No 8422353) were not conducted in compliance with GLP. However, the impact of the lack of GLP compliance of the validation methods to support bioanalysis/toxicokinetics in study Nos 8422349, 8422351 and 8422353 was later satisfactorily addressed by the Applicant.

Absorption

The results from two in vitro studies using Caco-2 cell monolayer assays, showed surufatinib to exhibit low permeability and to be a P-gp (and not BCRP) efflux transporter substrate.

Absorption kinetics of surufatinib after single dose i.v. or oral administration were characterized in Sprague-Dawley rats and Beagle dogs (non-GLP studies). Following an IV single dose (10 mg) or oral gavage (10, 40 and 160 mg/kg) in rats, plasma exposure of surufatinib was greater than dose-proportional in the dose range of 10-40 mg/kg and roughly dose-proportional from 40-160 mg/kg. After oral gavage, tmax was reached at 3.0-4.2 hrs (combined female/male data). The AUC0-t in female rats was 2.0 to 3.2-fold higher than in male rats, which corresponded to an approximately 2-fold lower plasma clearance in females (2.42 L/h/kg for females vs. 4.63 L/h/kg for males). Absolute bioavailability (combined female/male data) was estimated to be 9.9%, 72.4% and 67.8% after dosing of 10, 40 or 160 mg/kg, respectively, which may have reflected saturation of the P-gp efflux pump at doses ≥ 40 mg/kg. Following administration of oral capsules of surufatinib to male and female Beagle dogs at dose levels of 5, 10 or 20 mg/kg, tmax was reached within 3.5-4.5 hours postdose, and increases in Cmax and AUC0-t were roughly dose-proportional across the dose range. Clearance was high (3.94 L/h/kg). Bioavailiability of surufatinib in dogs ranged between 27.8%-44.3%, and there was no apparent effect of food on the PK in dogs. Contrary to what was seen in rats, sex differences did not influence PK in dogs.

After repeat oral administration of 40 mg/kg/day surufatinib in SD rats for 7 days, sex differences in kinetics were noted as seen after single-dosing (higher AUC0-t, Cmax and tmax in females compared to males). The mean accumulation ratio (combined male and female data) was 1.10- and 1.11-fold when comparing the mean Cmax and AUC0-24h from day 7 to those of day 1, indicating no accumulation after 40 mg/kg/day dosing of surufatinib in SD rats.

Three GLP-compliant repeat-dose TK studies were the basis of the assessment of the non-clinical studies performed in dogs and rats (study Nos 8422351, 8422349 and 8422353). Sex differences were observed in plasma exposure of surufatinib in rats (in line with observations from single-dose PK studies), whereas no sex differences in PK were observed in the repeated-dose study with surufatinib in dogs.

Following once-daily oral administration of 0, 5, 15 or 30 mg/kg of surufatinib to male and female rats for 13 weeks, tmax was reached after 4.0-8.0 hours (range covering female and male tmax).

Increases in doses from 5-15 mg/kg/day led to greater than dose-proportional exposure levels (based on AUC0-t) while approximate dose-proportionality was observed in the dose range of 15-30 mg/kg/day. High accumulation ratios were observed in the group dosed 5 mg/kg/day (ARfemale:23.3; ARmale:17.2). Moderate accumulation (AR: 2.3-5.9) was seen in rats dosed 15 or 30 mg/kg/day. Following oral repeat-dosing of 0, 2, 6 or 12 mg/kg/day surufatinib in male and female Beagle dogs for 13 weeks, tmax was reached after 2.0 hours. Exposure dose-proportionality was generally seen across the dose range (based on AUC0-t). Moderate accumulation was observed after repeat dosing at 12 mg/kg/day after 13 weeks (AR: 4.62).

Following once-daily oral gavage of surufatinib at 1, 4 and 15 mg/kg/day in pregnant SD rats (Study no: 8422353), exposure levels in the low-dose group were below LLOQ. From 4-15 mg/kg/day exposure levels of surufatinib increased with dose, and increases were greater than dose- proportional. Accumulation was noted in pregnant rats with both doses. The no observed adverse effect level (NOAEL) for maternal and fetal development was 4 mg/kg/day (corresponding to a GD17 Cmax and AUC0-t of 16.4 ng/mL and 125 h*ng/mL, respectively).

Accumulation appear not to be a concern in patients (Section 5.2, SmPC).

It should be noted that for the listed OECD/US GLP-compliant studies (8422349, 8422351, 8422353), the method validation reports (report no's: 8422-345 and 8422-346) were not in compliance with GLP. Please refer to Assessor's comment in Methods of analysis.

Exposure multiples based on exposures at NOAEL (or HNSTD) from OECD/US-GLP compliant studies conducted in rats and dogs and human exposure (based on clinical dose) showed low to non-existing safety margins for surufatinib.

Distribution

By means of rapid equilibrium dialysis the extent of plasma protein binding of surufatinib was shown to be moderate-to-high in different species including mouse (93.9 to 94.1%) rat (96.0 to 96.1%), dog (94.4 to 95.1%), monkey (93.5 to 93.6%) and human (95.9 to 96.0%) at a concentration range of 1 to 5 µM. Except in monkey at concentrations of 0.1 and 5 µM and in human at concentration of 1 µM, the recoveries of surufatinib after incubation in rapid equilibrium dialysis device were lower than 80% in almost all species thus this data is only for reference (study No DMPKR20140005-E-03).
The distribution of surufatinib was determined in mouse, rat, dog, monkey and human blood with an LC-MS/MS-based depletion method. The blood-to-plasma concentration ratio of 1 µM surufatinib was lowest in human, whereas surufatinib was distributed almost equally between blood and plasma in mouse and dog, and red blood cell distribution was higher in rat and monkey (study No DMPKR20190008-E-01). As the previous plasma protein binding study (study No DMPKR20140005-E-03) showed low post dialysis recoveries in almost all species except in human, the unbound fractions of surufatinib in blood is also only reliable in human and just for reference in other species.

A tissue distribution study using quantitative whole body autoradiography following a single oral dose of [14C]surufatinib in rats indicated that radioactivity was distributed extensively to tissues, and the total radioactivity was mainly distributed in metabolic, excretory, and endocrine systems. The highest levels of radioactivity were found in the liver, thyroid gland, adrenal cortex, adrenal gland, and the extra-orbital lachrymal gland. Radioactivity was distributed in the uveal tract, indicating binding to melanin-containing tissues. In addition, there was absorption in the UV visible spectrum. As a result, a phototoxicity study in guinea pigs was conducted. The low exposure of radioactivity in the brain suggested limited permeability at the blood-brain barrier (study No 14763).
The tissue distribution of surufatinib following a single oral administration to Sprague-Dawley rats was determined in collected biological samples by LC-MS/MS method. Surufatinib distributed to tissues rapidly and was detected with peak tissue concentrations occurring at 3 hours post dose. The higher

concentrations were observed in lungs, liver, spleen, adrenal gland, kidneys, pancreas and stomach. Surufatinib did not pass the blood-brain barrier markedly (study No HMPL-012-ADME-1).

No data on transplacental transfer of surufatinib was available.

Metabolism

Results from in vitro metabolism studies showed the predicted systemic clearance of surufatinib to be close to hepatic blood flow (indicating a high hepatic extraction of surufatinib) in all evaluated species (mouse, rat, dog, monkey, human). Higher predicted systemic clearance was noted for male rats compared to females (correlating with observations on sex differences in clearance from single-dose PK study in rats and the generally higher plasma exposures observed in female rats across repeat-dose in vivo studies), but not for other species. Species-related differences was observed, as dogs were the only species in which deactivation of FMO increased the in vitro t1/2 of surufatinib (i.e. FMO contributed to metabolism of surufatinib in dogs).
Five different metabolites (Mvitro1-Mvitro5) of surufatinib were detected in vitro after incubation with liver microsomes from different species (male mouse, rat, dog, monkey, human). No unique human metabolites were identified, and rats and dogs were chosen as species for toxicology studies. A CYP reaction phenotyping study involving incubation of surufatinib with human liver chromosomes in the presence or absence of monoclonal antibodies or chemical inhibitors for/of selected CYP isoforms, identified CYPs to be the primary enzyme system responsible for the metabolism of surufatinib (minimal metabolism when NADPH was absent) whereas the contribution by FMO was limited. Of the CYP isoforms evaluated, CYP3A4/5 was identified as the predominant contributor to surufatinib metabolism. When evaluating substrate depletion of surufatinib after 1-hour incubation with selected recombinant human CYP isoforms, CYP3A4 was determined as the predominant enzymes responsible for surufatinib metabolism (≥86.8% contribution), while contributions of remaining isoforms CYP3A5, CYP2D6 and CYP2C9 were ≤6.61%, 1.60% and 4.96%, respectively. As such, the potential of clinically relevant drug-drug interactions is present with use of surufatinib.

In vivo, the metabolism of surufatinib was evaluated after a single oral administration of 40 mg/kg [14C]surufatinib to rats. Surufatinib was extensively metabolized following oral gavage and eighteen metabolites of surufatinib were tentatively characterized or identified in rat plasma, bile, urine and/or feces. Neither of these metabolites were observed to have a plasma exposure (AUC0-24h) greater than 10% of total drug-related exposure, the threshold triggering non-clinical characterization of metabolites according to the ICH guideline M3(R2). The major phase I metabolic routes of surufatinib in rats included 1) carboxylation at the methyl group in the indole moiety, 2) N-demthylation, 3) mono-oxidation at multiple positions, 4) N-dephenylmethanesulfonamide. Main phase II metabolic pathways included glucuronidation and sulfation.

Excretion

Excretion was assessed in rats following oral administration of [14C]-surufatinib. In bile duct-intact rats, surufatinib was mainly excreted via feces (approximately 90% of the dose recovered in feces) and to a lesser extent via urine (approximately 5% of the dose). It was completely excreted within 120 hours post-dosing. In bile duct cannulated rats, feces, urine, and bile were collected up to 72 hours postdose. The total recovery of the radioactive material was approximately 93%, with approximately 43, 39, and 9% excreted in bile, feces, and urine, respectively. Overall, surufatinib was mainly excreted via the biliary/fecal route in rats after oral administration (study No XBLC14679N). In humans surufatinib was mainly excreted through feces (accounting for 87.85% of the dose) and a small amount was excreted from urine (accounting for 4.29% of the dose). The excretion of total radioactivity mainly occurred within 120 hours and accounted for approximately 90.12% of the dose (study No 2017-012-00CH1).

No data on milk transfer of surufatinib was available.

Pharmacokinetic drug interactions

Surufatinib showed weak reversible inhibition against CYP2B6 (study No DMPKR20190009-E-01), CYP2D6 (study No DMPKR20200033-E-01), and CYP3A4/5 (study No DMPKR20100072-02) without significant inhibitory effects on CYP1A2 (study No DMPKR20190009-E-01), CYP2C8, CYP2C9, and CYP2C19 (study No DMPKR20100072-02). Surufatinib was found to be a time-dependent inhibitor of CYP3A4/5 (study No DMPKR20140004-E-02). Surufatinib was a weak time-dependent inhibitor of CYP2B6 (study No DMPKR20190007-E-02) and CYP2D6 (study Nos DMPKR20200033-E-01 and DMPKR20190007-E-02) which is not is not expected to be clinically relevant. No induction was observed of CYP1A2, CYP2B6, or of CYP3A4 in human primary hepatocytes (study No 400253-20171120-HI).

In vitro data demonstrated that surufatinib was a P-gp substrate (study No DMPKR20120010-02), poor substrate of BCRP (study No 400253-20171120) and not a substrate of OAT1, OAT3, OCT2, MATE1, or MATE2-K transporters (study No 00253-20171120). Surufatinib was found to be an inhibitor of P-gp (study No DMPKR20170002-E-01) and BCRP (study No DMPKR20170003-E-01). As the predicted drug concentration in the gastrointestinal tract was high after oral administration surufatinib might affect the absorption of drugs that are P-gp or BCRP substrates. Surufatinib also inhibited OCT2 in HEK293 cells (study No 400253-20171120) and OATP1B1 and OAT1B3 in MDCKII cells (study No OPT-2019-216).

The potential for surufatinib to cause CYP-mediated or transporter-mediated pharmacokinetic drug interactions was determined by use of model-based predictions as described in the FDA's final Guidance for Industry: *In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (January 2020)* and suggested that:

> A clinically relevant drug interaction was found possible following co-administration of a CYP3A4 substrate but not for other major CYP isoforms including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6.
> Surufatinib might impact the absorption of concomitant P-gp and/or BCRP substrates, but not the exposure of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, or MATE2-K substrates.

These findings are reflected in section 4.5 of SmPC. A clinical study to evaluate the effects of surufatinib on the pharmacokinetics of substrates of CYP3A4, P-gp and BCRP is ongoing. No other pharmacokinetic drug interactions are expected.

Other pharmacokinetic studies
No other pharmacokinetic studies were conducted.

Toxicology

A number of toxicity studies were repeated, due to lack of OECD GLP compliance of the originally completed nonclinical studies. The 3-month rat and dog studies were repeated at Covance in Shanghai, the reproductive toxicity (definitive and DRF) EFD studies in rats were performed in United States and the genotoxicity study battery was performed in United Kingdom. The repeat-dose studies were performed at Covance in Shanghai which was inspected by Belgian authorities in, 2011, 2013, 2016, 2018 and 2020 (last inspection was remote due to COVID-19 restrictions) and was found to be GLP compliant.

Rats and dogs were judged appropriate species for pivotal nonclinical safety studies because the toxicity profile in rats and dogs, as derived from early repeat-dose non-pivotal toxicity studies with surufatinib, was considered in line with other tyrosine kinase inhibitors such as sunitinib and sorafenib.

Further, no unique human metabolite was observed in vitro from incubations with liver microsomes of various species, including rat and dog. In addition, extensive historical background data are available for these standard toxicology species.

Single dose toxicity

Single-dose toxicity after oral administration was performed in rats and dog. Only one dose level (2000 mg/kg) was used, and no control group was included in the dog study. In both species it was concluded that the dose level of 2000 mg/kg was the MTD (study Nos 0830AD1 and 083AD2). Since separate single-dose toxicity studies are not required anymore from a regulatory point of view, the Applicant informed that the single-dose toxicity studies were conducted in support of an NDA filing in China per "Guideline on Acute Toxicity Studies of Chemical Compounds" (issued by CFDA in May 2005) and were included in the MAA for completeness. The top-dose (2000 mg/kg) was selected based on criteria given in ICH M3 guideline. However, no toxicokinetics analyses were included in these single-dose studies and therefore, it is not known what extent of exposure margin to the clinical systemic exposure was attained with the used dose.

Repeat dose toxicity

Surufatinib was dosed repeatedly to rats (0, 5, 15 or 30 mg/kg/day) and dogs (0, 2, 6 or 12 mg/kg/day) for 13 weeks in two pivotal GLP-compliant toxicology studies (8422351 and 8422349).

Rat

In general, when dosed repeatedly to rats, surufatinib induced more adverse effects in females compared to males (correlating with the approximately 2-fold higher exposure in female rats, TK analysis). As such, the majority of toxicity findings in males were associated with a dose of 30 mg/kg/day; whereas changes were noted in females receiving both 15 and 30 mg/kg/day.

The primary target organs for surufatinib-related toxic effects were: hepatobiliary system, digestive system, immune system, hematopeoietic system and the skeletal system. No surufatinib-related toxic effects were noted on urinalysis, ophthalmic examinations or seminology, or in rats dosed 5 mg/kg/day. In general, most adverse effects were noted in the groups dosed with 30 mg/kg/day surufatinib, whereas surufatinib-related effects in rats dosed 15 mg/kg/day were considered non-adverse (abnormal teeth, mild body weight loss, reversible clinical pathology effects and decreased thymus weights). Overall, the endpoints investigated were reversible in rats, except for the broken teeth.

Based on the findings of study 8422351, the NOAEL was determined to be 15 mg/kg/day. The C_{max} was 452 ng/mL in males and 1060 ng/mL in females and the AUC_{0t} was 3810 ng•h/mL in males and 9850 ng•h/mL in females after administration of 15 mg/kg/day surufatinib for 91 consecutive days. In this 13-week rat study the NOAEL was determined to be 15 mg/kg/day although abnormal teeth (broken, malocclusion, or missing) were observed in 11 out of 15 females at this dose level. Teeth broken was not recovered at the end of the recovery phase. It is noted, that the Applicant's justification for setting 15 mg/kg/day as the NOAEL in the 13-week rat toxicology study can be considered questionable. The conclusion that abnormal teeth findings at this dose level in the absence of decreased food consumption and decreased body weight (gain) is nonadverse can be challenged. Decreased food consumption and decreased body weight gain may be related to digestive system toxicities including vomiting and diarrhea. Broken teeth are considered to be a result of skeletal system toxicity which was detected also as osteodysplasia in the femur and sternum and should not be assessed in the context of functional-related adverse effects.

Dog

After repeat-dosing of surufatinib to dogs, at 0, 2, 6 or 12 mg/kg/day for 13 weeks, surufatinib-related effects were primarily observed at the high dose (12 mg/kg/day), and were mainly associated with observations of abnormal feces (frequency male>female), decreased body weight and food consumption, and macroscopic/microscopic findings in 1 male at terminal sacrifice showing multiple red-discoloured foci in the mucosa of the distal colon, which correlated microscopically with minimal degeneration in the mucosal epithelium of the colon and multifocal congestion in the mucosa. Effects at the dose level of 6 mg/kg were generally minor, and considered non-adverse.

No surufatinib-related effects were observed in haematology, coagulation, clinical chemistry, urinalysis, ECG, or ophthalmic parameters. No surufatinib-related effects were observed in organ weights at the terminal or recovery sacrifice.

All findings were found to be reversible in the recovery phase.

Based on the findings of study 8422349, the NOAEL was determined to be 6 mg/kg/day in dogs. The C_{max} was 114 and 102 ng/mL and the AUC_{0t} was 934 and 756 ng•h/mL in males and females, respectively, after administration of 6 mg/kg/day surufatinib for 91 consecutive days.

NOAELs from NMPA-GLP repeat-dose toxicity studies of four weeks (rats and dogs), 26 weeks (rat) and 39 weeks (dog) with once-daily oral dosing of surufatinib.

The determined NOAELs from NMPA-GLP rat studies were 20 mg/kg/day at four weeks (corresponding AUC_{0-t}: 4540 ng*h/mL and 10600 ng*h/mL for males and females, respectively), and 5 mg/kg/day at 26 weeks (corresponding AUC_{0-t}: 1837 ng*h/mL and 1060 ng*h/mL for males and females, respectively). The NOAELs from NMPA-GLP dog studies were 12 mg/kg/day at four weeks (corresponding AUC_{0-t}: 696 ng*h/mL and 1142 ng*h/mL for males and females, respectively) and <2 mg/kg/day at 39 weeks (corresponding AUC_{0-t}: 223 ng*h/mL and 268 ng*h/mL, for males and females, respectively), indicating a reduced tolerability to surufatinib by prolongation of the dosing phase.

For reference, when including findings in the NMPA-GLP repeat-dose toxicity studies in rats and dogs, main target systems included the hepatobiliary system, gastrointestinal system, urinary system, immune system, hematopoietic system, skeletal system, enlarged adrenal glands, uterine atrophy and corpus luteum necrosis.

No significant new target organ system or adverse effects were noted in the two GLP-compliant studies (8422349, dogs and 8422351, rats) when comparing to the listed findings of the two superseded 13-week NMPA-GLP studies in rats (A201014-T011) and dogs (A201014-T012).

Toxicokinetics

TK parameters from the two pivotal 13-week GLP toxicology studies in rats and dogs, indicate a shorter t_{max} of surufatinib in dogs (2.0 hours) at all doses compared to rats (range: 4.0-8.0 hours).

Sex differences were observed in exposure (AUC_{0-t} and C_{max}) in rats, where exposures in females were ≥2-fold higher than those of males. Such sex differences were not seen after dosing of surufatinib to dogs, and together these observations correlate with the overall toxicology findings (i.e. more toxic effects of surufatinib noted in female compared to male rats, while no obvious sex differences were noted in terms of toxicity in dogs).

After 13 weeks of oral dosing of surufatinib to rats, increases in C_{max} and AUC_{0-t} were markedly greater than dose-proportional from 5-15 mg/kg/day, whereas dose-proportionality was seen when increasing dose from 15-30 mg/kg/day. In dogs, dose-proportionality was generally seen across the dose-range (2-12 mg/kg/day).

Accumulation was noted after 13 weeks of dosing in rats, with very high accumulation ratios at the low dose of 5 mg/kg/day (AR:17.2 for males and AR:23.3 for females), while low-to-moderate accumulation ratios were noted rats dosed 15 or 30 mg/kg/day (range of AR (male and female): 2.3 to 5.6). In dogs, no apparent accumulation was noted at 2 and 6 mg/kg/day, whereas moderate accumulation was noted at 12 mg/kg/day (AR: 4.62), which was however attributed to markedly lower exposure levels in two animals on day 1 of dosing.

In pregnant SD rats, surufatinib exposure (AUC_{0-t}) increased with dose and were greater than dose-proportional. Accumulation was noted after repeated dosing from GD6-GD17, and the NOAEL for maternal and fetal development was 4 mg/kg/day (corresponding to a GD17 C_{max} and AUC_{0-t} of 16.4 ng/mL and 125 h*ng/mL, respectively)

Margins of exposure

Comparison of exposure data from the two 13-week pivotal GLP-compliant toxicology studies in rats (8422351) and dogs (8422349) and the GLP-compliant repeat-dose EFD study in rats (8422353) to human exposure at the clinical dose, showed very low to non-existing safety margins for surufatinib. In most cases, the AUC exposure multiples were less than 1.

However, this can be supported as surufatinib is intended for the treatment of patients with advanced cancer. When administering tyrosine kinase inhibitors targeting receptors in rapidly dividing tissues, off-target toxicity in healthy dividing tissues is also expected.

Genotoxicity

The assessment of genotoxic potential of surufatinib was carried out in accordance with the ICH guideline S2(R1) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use.

Surufatinib was studied with respect to gene mutations in bacteria and chromosomal aberrations in mammalian cells and by conducting in vivo micronucleus test and alkaline comet assay in female rats. Neither the two in vitro tests nor the in vivo micronucleus test gave any indication for a mutagenic potential. In conclusion, surufatinib is not considered to be genotoxic (study Nos 8422605, 8422356 and 8422355).

Carcinogenicity

According to the ICH guideline S9 on Nonclinical Evaluation for Anticancer Pharmaceuticals carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer and thus the omission of carcinogenicity studies can be accepted, as the sought indication is indeed regarding advanced cancer therapy.

Reproductive and developmental toxicity

Reproductive and developmental toxicity of surufatinib was evaluated in Sprague-Dawley rats and New Zealand rabbits. For rats, these included: one NMPA-GLP study on fertility and early embryonic development (A201014-T031), and one non-GLP dose-range finding EFD study (8422352) to support an US FDA-GLP-compliant EFD study (8422353). In addition, one NMPA-GLP EFD study was performed in rabbits.

Assessment on effects of surufatinib on embryo-fetal development will primarily be based on the findings of the US FDA-compliant EFD study (8422353).

No studies on peri-and postnatal development were available, and this is acceptable according to ICH S9 guideline on Nonclinical Evaluation for Anticancer Pharmaceuticals.

Fertility and early embryonic development

Surufatinib-related effects on parental animals were evident by a high frequency of white, loose/crackled and/or fractured incisors at the high dose levels (45 mg/kg/day for males; 30 mg/kg/day for females). In addition, decreased body weight and food consumption was observed in males dosed 45 mg/kg/day. Mated females dosed 30 mg/kg/day exhibited lower body weight on GD15, and pregnant females (n=10) was observed to have a lower body weight gain from GD8-14 compared to control (n=18). These findings are overall consistent with reported findings from the 13-week repeat-dose toxicity study in rats dosed 30 mg/kg/day (8422351).

Only incidental pathological abnormalities were noted on male reproductive organs (1 rat with decreased size of left testis, 1 cystic nodule unilaterally in cauda epididymis). No abnormalities in mating rate, sperm motility/density or malformation rate was observed in males dosed with surufatinib. In agreement with these findings, no surufatinib-related effects on seminology were noted in the 13-week repeat-dose toxicity study in male rats (8422351).

No abnormalities were observed in the mating rate and sexual cycle length in females. At 30 mg/kg/day, mated females had reduction in total weight and organ-to-body weight ratios of the ovary and uterus, which was not observed in mated females dosed 3 or 10 mg/kg/day. In pregnant females dosed 30 mg/kg/day, decreased gravid uterus weight, uterus with placentas weight, total weight of viable fetuses, average weight of viable fetuses, absolute weight, and organ-to-body/brain weight ratios of uterus was noted. None of these abnormalities was noted in pregnant females dosed 3 or 10 mg/kg/day.

Females dosed 30 mg/kg/day had decreased conception rate (10/22, 45.5%) and pregnancy rate (4/10, 40%), and decreased number of corpora lutea, implantation sites, viable fetus numbers and increased total resorptions, preimplantation loss index, postimplantation loss index, total loss number, and total loss index compared to controls.

In summary, dosing of surufatinib at 30 mg/kg/day affected female fertility and early embryonic development in rats. The NOAEL of surufatinib was considered to be 15 mg/kg/day for parental male rats and 10 mg/kg/day for parental female rats. The NOAEL for male rats for fertility and early embryonic development was considered to be 45 mg/kg/day and the NOAEL for female rats for fertility and early embryonic development was considered to be 10 mg/kg/day.

Embryo-fetal development

An initial non-GLP dose-range finding EFD study was conducted (8422352) to support the subsequent US FDA GLP-compliant study in rats (8422353). Based on results of this dose-range finding study, it was recommended that dose levels for the subsequent definitive study No 8422353 in timemated rats were not to exceed 15 mg/kg/day, corresponding to a GD 17 C_{max} and AUC_{0t} of 717 ng/mL and 7600 ng•h/mL, respectively.

In study No 8422353, once daily oral gavage administration of 1, 4, or 15 mg/kg/day surufatinib to time-mated Sprague-Dawley rats during organogenesis (GD 6 through 17) resulted in maternal and fetal test article-related effects for the group administered 15 mg/kg/day. Surufatinib-related, adverse reductions in mean body weight gain were observed during dosing and mid-gestation, which corresponded with surufatinib-related, non-adverse, reductions in mean food consumption during mid-gestation. Adverse, Surufatinib-related, statistically significant, increased postimplantation loss, reduced gravid uterine weight, and reductions in adjusted mean fetal body weight were also noted for the group administered 15 mg/kg/day. Developmental toxicity was observed in fetuses of animal

administered 15 mg/kg/day as external, visceral, and skeletal anomalies. External anomalies consisted of edema, abnormal tail development, and malrotated limbs, and the visceral evaluation showed an increase in cardiovascular malformations of absent aortic arch, malpositioned subclavian artery, and retroesophageal subclavian artery. Skeletal evaluations showed surufatinib-related increases in sternebra and vertebral anomalies as well as increased incidence of supernumerary rib and unossified phalanx.

Exposure of surufatinib, assessed by TK parameters of C_{max} and AUC_{0-t}, generally increased with the increase in dose level from 4 to 15 mg/kg/day, and were greater than expected if dose proportional. Accumulation was observed after multiple doses in pregnant animals.

Based on the results from this study, the no observed adverse effect level (NOAEL) for maternal and fetal development was 4 mg/kg/day surufatinib (GD 17 C_{max} and AUC_{0-t} was 16.4 ng/mL and 125 h*ng/mL, respectively).

Prenatal and postnatal development, including maternal function

In accordance with ICH guideline S9 on Nonclinical Evaluation for Anticancer Pharmaceuticals no dedicated studies of surufatinib on prenatal and postnatal development were conducted and this is endorsed.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

Juvenile toxicity studies with surufatinib are ongoing and the completion of the studies is deferred in compliance with the paediatric investigation plan. This is accepted.

Local tolerance

The local tolerance of surufatinib was evaluated as part of the repeat-dose toxicology studies in rats and dogs. The endpoints in the local tolerance study were confined to clinical signs and macroscopic and microscopic examination at the application site in accordance with the ICH guideline M3(R2) which is accepted. Overall, expected findings were observed in the gastrointestinal trach in both rats and dogs. No further studies were required.

Other toxicity studies

Antigenicity

No studies on antigenicity were performed as surufatinib is a non-peptigenic chemical of low molecular weight. This is acceptable, as the risk of anti-drug antibodies formation in patients is considered to be low.

Immunotoxicity

Immunotoxicity evaluations were incorporated in the repeat-dose toxicity studies in rats and dogs. Based on the results of these studies and the clinical indication no follow-up studies were considered warranted. This approach is consistent with the ICH guideline S9 on Nonclinical Evaluation for Anticancer Pharmaceuticals where the design components of the general toxicology studies are considered sufficient to evaluate immunotoxic potential.

Dependence

No studies on dependence were performed as surufatinib was not active in the central nervous system. In addition, a safety pharmacology study on the central nervous system in rats (single-dose up to 120 mg/kg) indicated no adverse effect of surufatinib on neurological function.

Metabolites

No metabolites were identified that met the criteria for further evaluation. Thus, it was supported that no toxicological studies with surufatinib metabolite dosing were performed.

Studies on impurities

Surufatinib contained manufacturing impurities, that may be present at levels above the qualification threshold outlined in ICH Q3A(R2), 2006. The impurities both share the same structural alert as the drug substance, which was non-mutagenic in a standard genotoxicity battery. The impurities are considered qualified by the 13-week repeat-dose dog study and the in silico assessments using DEREK/Sarah.

Other studies

Phototoxicty

Surufatinib absorbs light in the wavelength range of 290 to 700 nm with molar extinction coefficients of the maximum absorptions above 1000 $L*mol^{-1}*cm^{1}$. Further, surufatinib showed distribution to the uveal tract in a rat whole-body autoradiography study. Surufatinib was evaluated in an in vivo study with guinea pigs to further evaluate its phototoxic potential. Surufatinib was not phototoxic at single doses up to 300 mg/kg (the highest dose employed). At a dose of 300 mg/kg, the AUC (combined genders) was 37,350 ng×hr/mL, which is 7.8-fold above the AUC at a clinical dose of 300 mg (4,770 ng×hr/mL) (study No 19186PT01).

Ecotoxicity/environmental risk assessment

The applicant has submitted an Environmental Risk Assessment for surufatinib, consisting of Phase I and Phase II studies.

In Phase I a PBT screening and a calculation of Fpen and PECSURFACEWATER values were performed. The LogDow did not exceed the threshold of 4.5, however the PECSURFACEWATER value exceeded the action limit of 0.01 µg/L, and hence a Phase II assessment was triggered. With regard to the already submitted Phase II studies, and those that are still lacking/ongoing (OECD 308, OECD 305), some concerns are raised below:

The Environmental Risk Assessment for surufatinib was conducted in accordance with the draft EMA guideline for the Environmental Risk Assessment of Medicinal Products for Human Use (CHMP/SWP/4447/00 REV 1, 15 November 2018). This is not acceptable, since the guideline EMEA/CHMP/SWP/4447/00 corr 2, June 2006 is currently in force and ERA shall be performed in accordance with this regulatory active guideline, not the unaccepted draft one. Surufatinib is not readily biodegradable thus requiring a degradation study in aqueous sediment systems (OECD 308). Further, in the Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/44609/2010 Rev. 1) it is clearly stated in Question No 9 ii) that the OECD 308 study cannot be waived by directly testing toxicity to sediment organisms: "*OECD 308 cannot be waived, since the test does not only give information on shifting of substances to the sediment, but also on half-life values, transformation products formed, mineralisation, and bound residue formation*". The Applicant is asked to submit the OECD 308 study.

Further, for submission of the bioaccumulation study (OECD 305) in 2Q 2023, a respective letter of agreement should be provided.

With regard to the Early Life Stage Toxicity Test in *Pimephales promelas* (OECD 210), the Applicant is asked to change the effect value EC50 to EC50>0.34 mg/L for the endpoint growth, since this concentration represents the highest concentration which included surviving organism.

Further, in the raw data of sublethal effects in OECD 210, the control groups already showed malformations occurring in the first days with increasing number over time. Formally, the control groups can not be considered healthy and thus are not acceptable as an appropriate comparison group. However, regarding the 3R-rule of animal welfare, the plausible performance of the study and the still detected effects, it is not considered necessary to submit a new OECD 210 study. Nonetheless, the Applicant is asked to provide an explanation (from the laboratory) for the poor physical condition of the control group (and thus possibly of their farmed fish) already seen at the beginning of the test.

With regard to the sediment dwelling study (OECD 218), the Applicant is asked to use the NOEC 835 mg/kg for the risk assessment, as concentration results from toxicity tests should only be recalculated into standard sediment with an organic carbon (o.c.) content of 10% if there is a correlation in the sewage sludge's organic carbon and the concentration of the substance in the aqueous phase at adsorption equilibrium obtained in the study on adsorption/desorption (OECD 106).

Finally, the Applicant is asked to discuss the reproductive toxicity substance properties of surufatinib with regard to the environmental risk assessment. The active substance surufatinib is suspected to cause both impairment of fertility and effects in reproductive toxicity studies in mammals. Therefore, it should be discussed whether this suspicion possibly also applies to wildlife organisms or not, e.g. fish.

If such effects on fertility and reproduction cannot be ruled out for wildlife organisms, a different test strategy should be followed. A fish early life stage test (OECD 210) as submitted may not provide the most relevant ecotoxicological information, since this test is rather short and it does not cover the relevant life stages like sexual maturation and reproduction. Thus, the design of a study should include the appropriate exposure time, the sensitive life-stage(s) and the relevant endpoints necessary to detect adverse effects and underlying modes of action. To detect reproductive toxicity a tiered testing strategy should be followed, e.g., an in vivo screening test (OECD 229 or OECD 230) may be performed. As stated in the test guidelines, both are screening tests only, and are therefore not suitable for a quantitative risk assessment. If effects are observed in such a test, long-term adverse effects should then be characterized in a fish sexual development test or a fish full life cycle test. Even if the mode of action is known, it may still be necessary to perform a fish full life cycle test, for instance, when the screening or partial lifecycle tests do not cover all endpoints or life stages, which are at risk. If the mode of action or the most sensitive endpoints are not known, a fish full life cycle study should be performed.

In conclusion, the two mentioned Phase II studies and a subsequent updated ERA should be submitted by the Applicant. Additionally, some concerns were raised regarding the already available Phase II studies, that should be addressed by the Applicant. Therefore the available data do not allow to conclude definitively on the potential risk of surufatinib to the environment.

Summary of main study results

Substance (INN/Invented Name): Surufatinib			
CAS-number (if available): Benzenemethanesulfonamide, *N*-[2-(dimethylamino)ethyl]-3-[[4-[(2-methyl-1*H*-indol-5-yl)oxy]-2-pyrimidinyl]amino]-			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH = 5 and Log D = 0.7 pH = 7 and Log D = 2.1 pH = 9 and Log D = 3.3	Potential PBT: No
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**

$PEC_{SURFACEWATER}$, refined (prevalence)	0.0525	µg/L			< 0.01 threshold: Yes
Other concerns (e.g. chemical class)	-	-			None
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Koc soil = 22710, 35685, 75031 Koc sludge = 2905+3014			No o.c. correlation
Ready Biodegradability Test	OECD 301	Biodegradation: 0 and 7%			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$= $DT_{50,\ sediment}$= $DT_{50,\ whole\ system}$= % shifting to sediment=			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ Raphidocelis subcapitata	OECD 201	NOEC	21	µg/L	-
Daphnia sp. Reproduction Test, *Daphnia magna*	OECD 211	NOEC	280	µg/L	-
Fish, Early Life Stage Toxicity Test, *Pimephales promelas*	OECD 210	NOEC	330	µg/L	-
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	1000 000	µg/L	-
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	NA	L/kg	Ongoing
Sediment dwelling organism	OECD 218	NOEC	835	Mg/ kg	Chironomus riparius

Discussion on non-clinical aspects

Pharmacology

Five in vitro pharmacology studies were conducted to determine the binding characteristics, functional activity and anti-angiogenic effects of surufatinib.

Surufatinib showed a strong, selective inhibitory effect on VEGFR family kinases, FGFR1, and CSF1R, with IC50s < 0.025 µM all of which play important roles in angiogenesis (study Nos study No 2014-012-01 and (study No 2014-012-02).
Surufatinib displayed weak inhibition of other kinases and had no meaningful inhibitory effect on the epidermal growth factor receptor (EGFR) suggesting less off-target cytotoxicity (study No 2014-012-02). This high selectivity and the associated potential for limited off-target toxicity differentiate surufatinib from other clinical anti-angiogenesis agents, including sorafenib and sunitinib (study Nos 2014-012-02 and 2014-012-08).
Experiments have demonstrated that surufatinib exerts a strong inhibitory activity on kinases of the VEGFR family and can block the activation of intracellular VEGFR2 and its downstream signaling pathways, thereby blocking VEGF-dependent HUVEC proliferation and lumen formation without obvious cytotoxicity (study No 2014-012-03). Surufatinib inhibited microvessel formation in a concentration-dependent manner in the rat aortic ring model with an IC50 of 192 nM (study No 2014-012-04). It was noted that the IC50 of 192 nM is approximately 5-fold greater than the unbound human steady-state Cmax for the proposed clinical dose of 300 mg/day surufatinib.

In mouse models, surufatinib completely inhibited the phosphorylation of VEGFR2 in lung tissues when the plasma drug concentration was greater than 181 ng/mL. The inhibition of phosphorylation was time- and dose-dependent, confirming surufatinib's on-target activity in vivo (study No 2014-012-07). Surufatinib showed notable inhibitory activity on the growth of multiple tumor types in the nude mouse model, with its inhibitory effect similar to that of sunitinib. The inhibitory effect of surufatinib demonstrated good dose dependence, and its degree of TGI was positively correlated with the exposure level (study No 2014-012-05).
Surufatinib also promoted dose-dependent antitumor angiogenesis in vivo (study No 2014-012-06).

Therefore, the in vitro and in vivo results suggest that surufatinib produced an inhibitory effect on the VEGFR signaling pathway and anti-angiogenic effects at multiple levels, thereby exerting an antitumor effect.
The role of surufatinib as a tumor immunomodulator was briefly described with reference to the literature in the non-clinical and pharmacology overviews however as no studies were presented in that regard this mode of action was not assessed.

The potential off-target secondary pharmacodynamic activity of surufatinib was characterized in vitro using selectivity assays against a panel of 87 enzymes, receptors and ion channels. Surufatinib at 3 μM demonstrated significant binding or inhibition on 11 targets (study No 100053308). When compared with the anticipated unbound maximum plasma concentration (Cmax) exposure (0.039 μM) in patients treated with surufatinib at 300 mg daily, the concentration associated with significant findings in the binding assay exceeded the clinical exposure by approximately 77-fold.

Safety pharmacology studies carried out in accordance with the ICH guidelines S7A and S7B was addressed with regards to effect of treatment with surufatinib on vital organ functions and indicated that the risk for adverse effects on the central nervous, respiratory and cardiovascular systems was low.

The OECD GLP hERG study showed that surufatinib inhibited hERG currents with an IC50 of 1.8 μM (study No 215-0075-EP), which is 46-fold above the clinical Cmax (free) at a dose of 300 mg, indicating a low risk for QTc prolongation.
Single oral administration of surufatinib up to 400 mg/kg, the highest dose employed, induced no adverse effects on motor activity, behaviour and coordination in ICR mice (study No 0830PB1).
In addition, no surufatinib-related effect was identified for respiratory rate, heart rate, QTc interval, P-R, or QRS values in an NMPA GLP compliant study in dogs (study No 0830PH1). However, the study was conducted in anaesthetised animals and as stated in ICH guideline S7A *"…it is preferable to use unanesthetized animals. Data from unrestrained animals that may be chronically instrumented for telemetry, other suitable instrumentation methods for conscious animals, or animals conditioned to the laboratory environment are preferable to data from restrained or unconditioned animals"*. Prior to recording respiratory and cardiovascular endpoints animals were anaesthetised in sodium pentobarbital, instrumented and inserted with catheters. Anaesthesia or surgery without sufficient analgesia is well known to cause profound effects on the respiratory and cardiovascular system. It was also noted that the only respiratory endpoint was the respiratory rate. Thus, the scientific contribution of this study appears limited.
In the repeated 13-week OECD GLP study in dogs, no abnormal ECG waveforms or arrhythmias were attributed to surufatinib based on a qualitative assessment (study No 8422349). The study was carried out in accordance with Scientific Advice, where CHMP requested that safety pharmacology assessments should be included in the OECD GLP repeat-dose toxicology studies.

Based on three subsequently conducted OECD GLP safety pharmacology studies, no effects on the respiratory (study No 8459960) or central nervous systems (study No 8459966) of rats were observed at doses up to 120 mg/kg. No clinically relevant changes in cardiovascular function in dogs were

observed up to the maximum dose of 60 mg/kg (study No 8459967). However, in the cardiovascular study No 8459967 the Applicant should comment on the treatment-related changes seen in diastolic, mean arterial and arterial pulse pressure. In addition, as study No 8459967 claimed GLP the Applicant is asked to comment on the lack of GLP compliance for the bioanalytical, pharmacokinetic, electrocardiographic and statistical analytical phase reports. No pharmacodynamic drug interaction studies with surufatinib were warranted as there were no drugs anticipated to be co-administered where a pharmacodynamic interaction was considered likely to occur.

Pharmacokinetics

Pharmacokinetics of surufatinib was studied in four studies in Sprague-Dawley rats and Beagle dogs after single i.v. or oral (oral gavage or capsules) administration (study Nos P-HMPL-012-ADME-1_RPK, RP-HMPL-012-ADME-1_DPK1, RP-HMPL-012-ADME-1_DPK1, DMPKR20120011-04 and XBLC14679N). The toxicokinetics of surufatinib in rat and Beagle dog after repeated administration were assessed from two pivotal toxicology studies (study Nos 8422351 and 8422349) carried out in accordance with GLP consistent with the ICH guideline S3A. The rat and Beagle dog, were selected as the relevant test species in the pivotal toxicology studies.

In the course of the non-clinical development several different LC/MS/MS assays were developed and validated for the quantitation of surufatinib in different species including rats, rabbits, dogs and guinea pigs. The key elements necessary for the validation of these bioanalytical methods as stated in the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**) were not fulfilled. In addition, the method validations were not GLP compliant. From the guideline: *"…the validation of bioanalytical methods used in non-clinical pharmacotoxicological studies that are carried out in conformity with the provisions related to Good Laboratory Practice should be performed following the Principles of Good Laboratory Practice. Aspects of method validation not performed according to GLP should be clearly identified and their potential impact on the validation status of the method indicated"*.

The bioanalytical methods (study Nos 8422-345 and 8422-346) validated to support the bioanalysis in the pivotal toxicology studies in dogs and rats (study Nos 8422349 and 8422351) and the embryo-fetal development study in rats (study No 8422353) were not conducted in compliance with GLP. The methods were fully validated in accordance with the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**) with regard to selectivity, carry-over, sensitivity, calibration, accuracy, precision, dilution integrity, matrix effect and stability. The impact of the lack of GLP compliance of the validation methods to support bioanalysis/toxicokinetics in study Nos 8422349, 8422351 and 8422353 was later satisfactorily addressed by the Applicant.

The assessment of surufatinib pharmacokinetics following a single oral dosing of surufatinib in rats and dogs showed relatively slow oral absorption, high clearance, and high volume of distribution. The oral absorption might have been affected by the efflux transporter P-gp at low doses. The absolute oral bioavailability was 9.9 and 30.5% at 10 mg/kg in rats and dogs, respectively. In dogs increases in Cmax and AUC0-t were roughly dose-proportional over the dose range 5 to 20 mg/kg. After single dosing plasma exposure in rats was higher in female animals compared to males however no sex differences were observed in dogs (study Nos XBLC14679N, P-HMPL-012-ADME-1_RPK, RP-HMPL-012-ADME-1_DPK1 and DMPKR20120011-04). See further toxicokinetic studies in repeat-dose toxicity.

Plasma protein binding was shown to be moderate-to-high in different species including mouse, rat, dog, monkey and human ranging from 93.5 to 96.0%. This data was only for reference for mouse, rat, and dog as the recoveries of surufatinib after incubation in rapid equilibrium dialysis device for these species were lower than 80%. Blood cell distribution of surufatinib was lowest in human, almost equally between blood and plasma in mouse and dog, and red blood cell distribution was higher in rat and monkey (study No DMPKR20190008-E-01). As the previous plasma protein binding study showed

low post dialysis recoveries in almost all species the unbound fractions of surufatinib in blood is also only reliable in monkey and human and just for reference in other species.

A tissue distribution study using quantitative whole body autoradiography following a single oral dose of [14C]surufatinib in rats indicated that radioactivity was distributed extensively to tissues, and the total radioactivity was mainly distributed in metabolic, excretory, and endocrine systems. Radioactivity was distributed in the uveal tract, indicating binding to melanin-containing (study No HMPL-012-ADME-1). Therefore, the phototoxic potential of surufatinib was evaluated in a phototoxicity study. No data on transplacental transfer of surufatinib was available.

Similar in vitro metabolism was observed in liver microsomes across various species (mouse, rat, dog, monkey, and human). There was no human unique metabolite in vitro (study No MPKR20100074-02) and surufatinib was mainly metabolized by CYPs in human liver microsomes, predominantly via CYP3A4/5 (study No DMPKR20180023-E-01). The major metabolic pathway observed in rats was the carboxylation (study No XBLC14688N - RTC00603).

Following oral administration to rats, [14C]-surufatinib was mainly excreted via feces (approximately 90% recovered in feces including approximately 40% in bile) and to a lesser extent via urine (approximately 5% of the dose) (study No 2017-012-00CH1). No data on milk transfer of surufatinib was available.

Surufatinib had a time-dependent inhibitory effect on CYP3A4/5 (study Nos DMPKR20200033-E-01 and DMPKR20140004-E02) and inhibitory effects on transporters P-gp (study No DMPKR20170002-E-01) and BCRP (study No DMPKR20170003-E-01), suggesting a risk of drug interactions if co-administered with substrates of these transporters. A clinical study to evaluate the effects of surufatinib on the pharmacokinetics of substrates of CYP3A4, P-gp, and BCRP is ongoing.

Toxicology

Rats and dogs were judged appropriate species for pivotal non-clinical safety studies because the toxicity profile in rats and dogs, as derived from early repeat-dose non-pivotal toxicity studies with surufatinib, was considered in line with other tyrosine kinase inhibitors such as sunitinib and sorafenib. Further, no unique human metabolite was observed in vitro from incubations with liver microsomes of various species, including rat and dog. In addition, extensive historical background data are available for these standard toxicology species.

The toxicological profile of surufatinib for the sought therapeutic indication was characterized in single-dose toxicity studies in rats and dogs, repeat-dose toxicity studies in rats and dogs, a battery of in vitro and in vivo genotoxicity studies, a toxicity study on fertility and early embryonic development in rats, embryo-fetal developmental toxicity studies in rats and rabbits, and a phototoxicity evaluation in guinea pigs. Repeat-dose toxicity (13-week toxicity studies in rats and dogs) (study Nos 8422351 and 8422349), an embryo fetal toxicity study in rats (study No 8422353), and a standard battery of genotoxicity tests (study Nos 8422605, 8422356 and 8422355) were repeated under US FDA and/or OECD GLP regulations, due to lack of OECD GLP compliance of the originally completed nonclinical studies. These bridging studies superseded the comparable studies conducted under NMPA GLP regulations. All non-OECD GLP compliant studies are considered supportive in nature only.

In single-dose toxicity after oral administration was performed in rats and dog it was concluded that the dose level of 2000 mg/kg was the MTD (study Nos 0830AD1 and 083AD2).

In 13-week repeat-dose toxicity studies in rats (study No 8422351) and dogs (study No 8422349) surufatinib was administered once daily and NOAELs were determined to 15 and 6 mg/kg/day, respectively. The main target organs for surufatinib-induced toxic effects in rats included the hepatobiliary, digestive, immune, haematopoietic and the skeletal systems. More adverse effects were

observed in females compared to males correlating well with the approximately 2-fold higher exposure seen in female rats at the toxicokinetic analysis. Overall, the endpoints investigated were reversible in rats, except for the broken teeth. In dogs, treatment-related effects were mainly associated with observations of abnormal feces, decreased body weight and food consumption. All findings were found to be reversible in the recovery phase. No new target organ system or adverse effects were noted when comparing to the listed findings of the two superseded 13-week non-GLP studies in rats (study No A201014-T011) and dogs (study No A201014-T012). For reference, when including findings in the NMPA GLP repeat-dose toxicity studies in rats and dogs, main target organ systems included the hepatobiliary system, gastrointestinal system, urinary system, immune system, hematopoietic system, skeletal system, enlarged adrenal glands, uterine atrophy and corpus luteum necrosis. The above toxicity findings are consistent with similarly targeted drugs on the market. Effects on the hepatobiliary, renal, haematopoietic and digestive system were also noted in clinical trials with surufatinib but data reflect a manageable safety profile in the context of the proposed indication.

Toxicokinetic data from the repeat-dose studies in rats and dogs showed sex differences in exposure (AUC(0-24) and Cmax) in rats but not in dogs which increased in a roughly dose-proportionally manner in both species. Accumulation was moderate to high and moderate in rats and dogs, respectively. Surufatinib had very low to non-existing safety margins. This is accepted as NOAEL or NOEL are not considered essential to support clinical use of an anti-cancer pharmaceutical.

Genotoxicity studies were carried out in accordance with the ICH guideline S2(R1) and surufatinib showed no genotoxic potential (study Nos 8422605, 8422356 and 8422355).

No carcinogenicity studies were conducted as the sought indication of surufatinib was for advanced cancer therapy in agreement with ICH guideline S9.

In accordance with ICH guideline S9 no dedicated studies of surufatinib on fertility and early embryonic and prenatal and postnatal development were performed. Juvenile toxicity studies with surufatinib are ongoing and the completion of the studies is deferred in compliance with the paediatric investigation plan. In a repeat-dose study surufatinib at 30 mg/kg/day affected female fertility and early embryonic development in rats. The NOAEL for fertility and early embryonic development was considered to be 45 and 10 mg/kg/day for males and females, respectively (study No 8422351). A GLP compliant embryo-fetal developmental study conducted in orally dosed rats led to treatment-related findings of increased postimplantation loss, reduced gravid uterine weight, and reductions in adjusted mean fetal body weight. The NOAEL of surufatinib for maternal and fetal development was 4 mg/kg/day. A dose resulting in plasma exposures (AUC) 0.026-fold compared to the human exposure values. No further studies on developmental toxicity were performed in accordance with ICH guideline S5(R3).

The local tolerance of surufatinib evaluated as part of the repeat-dose toxicology studies consistent with the ICH guideline M3(R2) showed expected findings in the gastrointestinal tract in both rats and dogs. No further studies were required.

No studies on antigenicity were performed as surufatinib is a non-peptigenic chemical of low molecular weight. Thus, the risk of anti-drug antibodies formation in patients is considered to be low.

Immunotoxicity evaluations were incorporated in the repeat-dose toxicity studies in rats and dogs (rats: 4 weeks, 13 weeks, and 26 weeks; dogs: 4 weeks, 13 weeks, and 39 weeks; and rats and dogs: 13-week OECD GLP toxicity studies). Based on the results of these studies and the clinical indication no follow-up studies were considered warranted consistent with the ICH guideline S9.

No studies on dependence were performed as surufatinib was not active in the central nervous system. In addition, a safety pharmacology study on the central nervous system in rats (single-dose up to 120 mg/kg) indicated no adverse effect on neurological function.

No metabolites were identified that met the criteria for further evaluation. Thus, it was supported that no toxicological studies with surufatinib metabolite dosing were performed.

No concern regarding impurities were identified.

Surufatinib was evaluated as not phototoxic in a study with guinea pigs (study No 19186PT01).

The available data did not allow to conclude definitively on the potential risk of surufatinib to the environment as the OECD 308 was missing and final Phase II studies required in the Environmental Risk Assessment were ongoing (OECD 305). Further, some points for further clarification and discussion by the Applicant was requested. The applicant should commit to submitting the missing OECD studies and provide an updated ERA, including a discussion/clarification of the concerns raised by the Rapporteurs.

Conclusion on non-clinical aspects

Overall, the primary pharmacodynamic studies provided adequate evidence that surufatinib is a potent multikinase inhibitor targeting vascular endothelial growth factor receptor 1, 2, and 3; fibroblast growth factor receptor-1; and colony-stimulating factor-1 receptor with high specificity. The general pharmacology studies showed surufatinib inhibited activity on kinases of the VEGFR family, microvessel formation, blocked the activation of intracellular VEGFR2 including its downstream signalling pathways and inhibited activity on the growth of multiple tumor types in the nude mouse model. Thus, proof of concept, mechanism of action and mode of action were demonstrated. The potential off-target secondary pharmacodynamic activity of surufatinib was determined to be low. No safety pharmacological concern was identified at clinically relevant doses. Based on three subsequently conducted OECD GLP safety pharmacology studies, no effects on the respiratory or central nervous systems of rats were observed. No clinically relevant changes in cardiovascular function in dogs were noted. Studies on pharmacodynamic drug interactions were omitted.

From the pharmacokinetic point of view, the rat and dog were the most relevant species for non-clinical efficacy and safety studies. The pharmacokinetic data after single oral dosing of surufatinib in rats and dogs showed relatively slow oral absorption, high clearance, and high volume of distribution. The absolute oral bioavailability was 9.9 and 30.5% at 10 mg/kg in rats and dogs, respectively. In dogs increases in Cmax and AUC0-t were roughly dose-proportional over the dose range 5 to 20 mg/kg. After single dosing plasma exposure in rats was higher in female animals compared to males however no sex differences were observed in dogs. Blood cell distribution of surufatinib was lowest in human, almost equally between blood and plasma in mouse and dog, and red blood cell distribution was higher in rat and monkey. Plasma protein binding was shown to be moderate-to-high in different species. Radiolabeled surufatinib was extensively distributed throughout the body of rats. It has a high clearance rate and is mainly excreted via bile and feces in rats. Surufatinib is primarily metabolized by CYP3A4/5. Surufatinib has a time-dependent inhibitory effect on CYP3A4/5, and inhibitory effects on transporters P-gp and BCRP, suggesting the risk of drug interactions if co-administered with substrates of these transporters. A clinical study to evaluate the effects of surufatinib on the pharmacokinetics of substrates of CYP3A4, P-gp and BCRP is ongoing.

Overall, the toxicology program of surufatinib revealed no major concerns. The toxicity studies supporting the market authorization of surufatinib for the treatment of adult patients with low or intermediate grade (grade 1 (G1) or grade 2 (G2)) progressive neuroendocrine tumours of extrapancreatic or pancreatic origin that are locally advanced or metastatic were performed according to appropriate ICH guidelines. Toxicities in target organs including the hepatobiliary, digestive, immune, haematopoietic and the skeletal systems were seen in the rat and dog OECD GLP repeat-dose toxicity studies. Toxicokinetic data from the repeat-dose studies in rats and dogs showed sex

differences in exposure (AUC(0-24) and Cmax) in rats but not in dogs which increased in a roughly dose-proportionally manner in both species. Accumulation was moderate to high and moderate in rats and dogs, respectively. Surufatinib had very low to non-existing safety margins. Surufatinib was not considered to be genotoxic. Developmental toxicity, including embryo-fetal toxicity and teratogenicity was seen after treatment with surufatinib. No concern regarding antigenicity, immunotoxicity, dependence, metabolites and impurities were identified. Surufatinib was found to be non-phototoxic. The available data did not allow to conclude definitively on the potential risk of surufatinib to the environment.

In conclusion, no major objections were identified in the non-clinical dossier, however a number of questions have been raised, which need to be sufficiently addressed before approval of surufatinib can be supported from a non-clinical view.

Clinical aspects

- **Tabular overview of clinical studies**

Table 1. Clinical Studies relevant to surufatinib Clinical Pharmacology

Study Number	Study Title	Formulation	Section
Healthy Subject Pharmacokinetic Studies			
2016-012-00CH2	A Clinical Trial to Explore the Pharmacokinetics and Relative Bioavailability of Sulfatinib Capsules in Two Different Manufacturers in Chinese Adult Male Healthy Volunteers	Formulation 2 Formulation 3	Module 2.7.1, Section 2.2.1
2017-012-00CH1	A Single-Center, Open-Label, Single-Dose Clinical Trial to Study the in Vivo Mass Balance of Healthy Chinese Male Volunteers After Oral Administration of 300 Mg/100 μCi [^{14}C] Surufatinib Suspension	Study-specific formulation	Section 2.1.2
Patient Pharmacokinetic Studies			
2009-012-00CH1	Phase I Study of HMPL-012 in Patients with Malignant Solid Tumors	Formulation 1 Formulation 2	Section 2.2.1
2014-012-00CH1	A Multi Center, Open Label, Phase Ib/II Clinical Trial to Evaluate the Preliminary Efficacy, Safety, Tolerability, and Pharmacokinetics of Sulfatinib in Treating Advanced Neuroendocrine Tumors (NETs)	Formulation 2 Formulation 3	Section 2.2.2
2015-012-00US1	A Multicenter, Open-Label, Clinical Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Surufatinib (HMPL-012), Previously Named Sulfatinib in Advanced Solid Tumors	Formulation 2 Formulation 3	Section 2.2.3
Intrinsic Factor Studies			
2020-012-00US2	A Phase 1 Study to Assess the Effect of Hepatic Impairment on the Pharmacokinetics of Surufatinib (ongoing)	Formulation 3	Section 2.3.1
2020-012-00US3	A Phase 1 Study to Assess the Effect of Moderate Renal Impairment on the Pharmacokinetics of Surufatinib (ongoing)	Formulation 3	Section 2.3.2
Extrinsic Factor Studies			
2014-012-00CH2	A Randomized, Open-Label, Cross-Over Clinical Study of the Effect of Food on the Pharmacokinetics of Single-Dose Sulfatinib Capsules in Healthy Subjects	Formulation 2	Module 2.7.1, Section 2.3.1
2019-012-00US1	A Phase 1, Two Period Crossover Study to Assess the Effect of a High Fat Meal on the Pharmacokinetics of Surufatinib in Healthy Subjects	Formulation 3	Module 2.7.1, Section 2.3.2
2019-012-00US2	A Phase 1, Two Period Fixed-Sequence Crossover Study to Assess the Effect of Itraconazole, a Strong CYP3A Inhibitor, on the Pharmacokinetics of Surufatinib in Healthy Subjects	Formulation 3	Section 2.4.2.1
2020-012-00US1	A Phase 1, Open-label, 2 Part, 2 Period Fixed-Sequence Crossover Study to Assess the Effect of Rabeprazole, a Proton Pump Inhibitor, and the Effect of Rifampin, a Strong CYP3A Inducer, on the Pharmacokinetics of Surufatinib in Healthy Subjects	Formulation 3	Section 2.4.2.2

Study Number	Study Title	Formulation	Section
2020-012-00EU1	An Open-Label Phase 2 Study of Surufatinib in Patients with Neuroendocrine Tumours in Europe (ongoing) Note: The EU1 study contains 2 clinical pharmacology components: 1) a cohort to assess the effect of surufatinib on the PK of substrates of CYP3A4, P-gp, and BCRP 2) the effect of surufatinib on QTc intervals	Formulation 3	Section 2.4.2.3
HUMP/1/A	Development of a PBPK Model for Evaluation of Surufatinib Drug-Drug Interaction Liability as a Victim of CYP3A4 Inhibition/Induction and Perpetrator of CYP3A4, P-gp, and BCRP	NA (data from studies using formulation 2 and formulation 3)	Section 2.4.2.4
Phase 3 Studies			
2015-012-00CH4 (SANET-ep)	A Randomized, Double-Blind, Multicenter Phase III Clinical Study to Assess the Efficacy and Safety of Sulfatinib Compared to Placebo in Patients with Advanced Extrapancreatic Neuroendocrine Tumors	Formulation 2 Formulation 3	Section 2.5.1
2015-012-00CH3 (SANET-p)	A Randomized, Double-blind, Multicenter Phase III Clinical Study to Assess the Efficacy and Safety of Surufatinib Compared to Placebo in Patients with Advanced Pancreatic Neuroendocrine Tumors	Formulation 2 Formulation 3	Section 2.5.2

Study Number	Study Title	Formulation	Section
Pharmacometric Studies			
HMPI-PMX-SURU-2293 PopPK	Population PK, Exposure-Response, and Concentration-QTc Analyses of Surufatinib (Population-based PK modeling including data from 2014-012-00CH1, 2015-012-00US1, SANET-ep, and SANET-p studies and determination of significant covariates on surufatinib PK)	NA (data from studies using formulation 2 and formulation 3)	Section 2.6.1.1
HMPI-PMX-SURU-2293 Exposure-response	Population PK, Exposure-Response, and Concentration-QTc Analyses of Surufatinib (Exposure-efficacy relationships: exposure from PopPK and efficacy from SANET-ep, SANET-p, and 2015-012-00US1 studies; Exposure-safety relationships: exposure from PopPK and safety from 2014-012-00CH1, 2015-012-00US1, SANET-ep and SANET-p studies)	NA (data from studies using formulation 2 and formulation 3)	Section 2.6.1.2
HMPI-PMX-SURU-2293 Concentration-QTc analysis	Population PK, Exposure-Response, and Concentration-QTc Analyses of Surufatinib (Concentration-QTc analysis based on data from Study 2015-012-00US1)	NA (data from studies using formulation 2 and formulation 3)	Section 2.6.1.3

BCRP=breast cancer resistance protein; CYP=cytochrome P450; EU=European Union; NA=not applicable; NET=neuroendocrine tumor; PBPK=physiologically based pharmacokinetics; P-gp=P-glycoprotein; PK=pharmacokinetics; popPK=population pharmacokinetic; sulfatinib=surufatinib; QTc=heart rate-corrected QT interval.

Clinical pharmacology

Pharmacokinetics

Surufatinib (HMPL-012, previously known as sulfatinib) is a small molecule kinase inhibitor), which inhibits vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3; fibroblast growth factor receptor-1 (FGFR-1); and colony-stimulating factor-1 receptor (CSF1R).

The proposed indication is treatment of adult patients with low or intermediate grade (G1 or G2) progressive neuroendocrine tumours of extrapancreatic or pancreatic origin that are locally advanced or metastatic. To date, 15 clinical studies with surufatinib have been conducted (6 in healthy volunteers and 9 in patients with cancer). Of the 15 clinical studies, 11 were conducted in China and 4 were conducted in the US, including Study 2015-012-00US1, an ongoing phase 1 study in the United States designed to bridge data from patient populations treated in China to treatment options available in the West. An overview of the clinical program and clinical studies supporting the clinical pharmacology summary is presented in Table 1 above.

Dose rationale

The proposed commercial product of surufatinib is a 50-mg capsule, and the recommended dose is 300 mg orally once daily (QD). The selected dose and dosing schedule for surufatinib were determined from Studies 2009-012-00CH1, 2014-012-00CH1, and 2015-012-00US1, and were confirmed by 2 phase 3 studies (SANET-ep and SANET-p) showing improvement in investigator-evaluated PFS in patients with epNET and pNET, as well as an acceptable safety profile in the surufatinib arm as compared to the placebo arm.

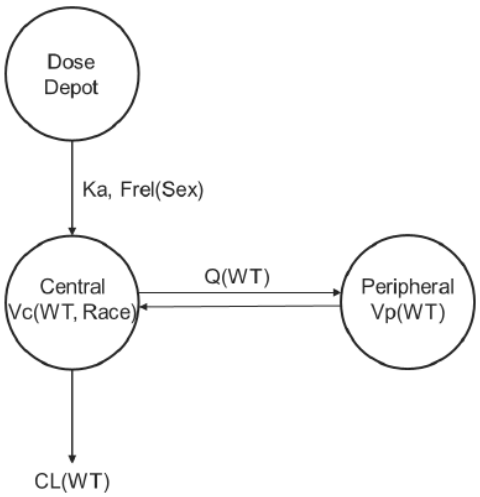
Bioanalysis

Surufatinib was quantitated in human plasma by validated protein precipitation - LC-MS/MS methods. Three methods were validated. The initial LC-MS/MS method used for the human FIH study (Study 2009-012-00CH1, formulation 1) was insufficiently validated. A second LC-MS/MS method which included further validation testing was used for sample analysis in Study 2009-012-00CH1, formulation 2. A third LC-MS/MS method (HM12HPP) was validated at two CRO sites. The HM12HPP method was used for quantification of surufatinib in the majority of clinical studies. A structural analoque of surufatinib with comparable physical-chemical properties was used as internal standard.

PopPK analyses

The final population PK model for surufatinib was a 2-compartment model with linear elimination, first-order absorption, lag time with residuals described by an additive error model (fixed to 0.001) and a proportional error model. IIV was applied on CL and V terms with a full block covariance matrix.

Appendix 1.2.5 Schematic of Final Population PK Model for Surufatinib



CL = clearance; Frel = relative bioavailability; Ka = first-order absorption rate constant; Q = inter-compartmental clearance; Vc = central volume of distribution; Vp = peripheral volume of distribution; WT = body weight.

The Pop PK analyses included data from patients with NET, pNET, epNET or advanced solid tumors from studies 2014-012-00CH1 (N=81), SANET-p (N=195), SANET-ep (N=273), and 2015-012-00US1 (N=152). No data from healthy subjects were included. Of 3907 observations, 3768 were quantifiable from 385 subjects and included in the population PK analysis. BLQ samples were excluded. Allometric scaling of body weight was included on disposition parameters using fixed standard exponents. The effect of sex on the relative bioavailability and the effect of race on Vc/F were the only significant covariates.

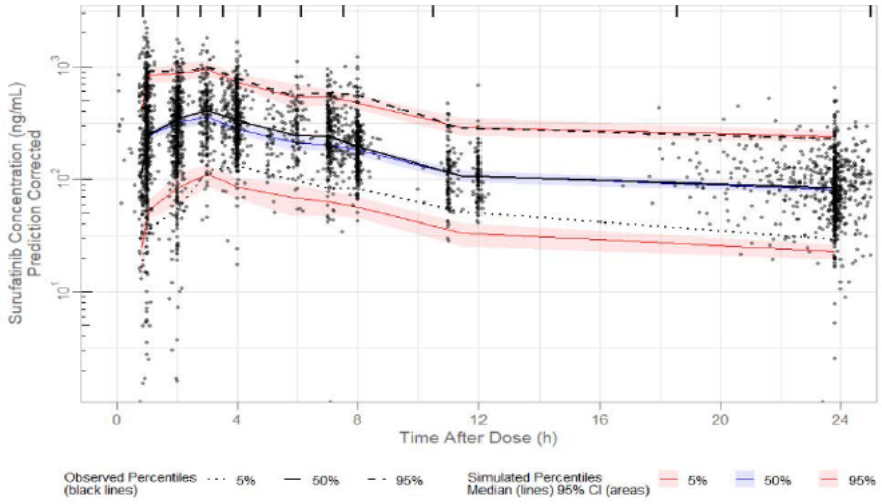
Table 2. Bootstrap Results for the Final Population PK Model

Parameter	Estimate	RSE	Bootstrap Median	Bootstrap 95% CI
Fixed effects				
Apparent clearance (70 kg), CL/F (L/h)	74.8	3.7%	74.7	69.3, 80.2
Apparent central compartment volume (70 kg, Asian), Vc/F (L)	189	9.3%	191	159, 227
Apparent peripheral compartment volume (70 kg), Vp/F (L)	1642	5.8%	1641	1460, 1834
Apparent inter-compartmental clearance (70 kg), Q/F (L/h)	90.3	4.6%	90.3	82.4, 98.6
First-order absorption rate constant, Ka (1/h)	0.286	3.0%	0.286	0.271, 0.304
Time lag, Tlag (h)	0.704	2.0%	0.705	0.673, 0.725
Covariate effects				
Fractional change in bioavailability for females	+0.176	34.4%	+0.175	+0.053, +0.308
Fractional change in Vc/F for races other than Asian	-0.375	26.4%	-0.377	-0.550, -0.146
IIV				
IIV CL/F variance	0.253	8.6%	0.249	0.211, 0.294
IIV Vc/F variance	1.49	9.8%	1.47	1.23, 1.78
IIV Vp/F variance	0.287	16.8%	0.280	0.187, 0.382
IIV Q/F variance	0.221	14.0%	0.218	0.161, 0.282
IIV covariances				
Covariance(CL/F, Vc/F)	0.181	22.1%	0.178	0.101, 0.258
Covariance(Vp/F, CL/F)	0.177	14.9%	0.174	0.124, 0.228
Covariance(Vp/F, Vc/F)	0.101	69.5%	0.100	-0.027, 0.235
Covariance(Q/F, CL/F)	0.205	10.2%	0.203	0.163, 0.244
Covariance(Q/F, Vc/F)	0.134	39.2%	0.130	0.019, 0.226
Covariance(Q/F, Vp/F)	0.207	14.6%	0.203	0.146, 0.266
Residual variability				
Proportional error CV%	0.353	2.4%	0.352	0.336, 0.368
Additive error SD (ng/mL)	0.001 FIXED	N/A	0.001 FIXED	N/A

CI = confidence interval; CV = coefficient of variation; IIV = inter-individual variability; N/A = not applicable; RSE = relative standard error; SD = standard deviation.

The final parameters were estimated with good precision and low eta shrinkages. The bootstrap results were close to the parameter estimates and none of the CIs contained the null, except for the IIV of covariance for volumes which also had high RSE. The GoF plots did not indicate any major trends. The VPCs could adequately capture the mean of observed data.

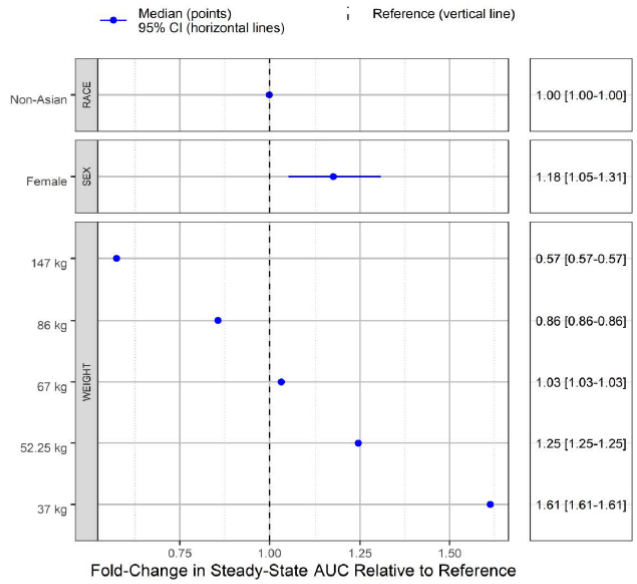
Figure 1. Visual predictive Check for the Final Population PK Model



Notes: Black dots are observed data points; the red solid line is the observed median; the red dotted and dashed lines are the observed p5 and p95, respectively. The blue shaded region is the 95% PI of the simulated median, and red shaded regions are the 95% PI of the simulated p5 and p95.
CI = confidence interval; p5 = 5th percentile; p95 = 95th percentile; PI = prediction interval; PK = pharmacokinetic.

Impact of covariates on exposure parameters were tested at 300 mg QD surufatinib across the demographic span in the Pop PK population and displayed in Forest plots. Race had no impact on exposure while females experienced slightly higher exposures than men, but the effect was within the 1.25 limit and not considered clinically relevant. Weight, which was allometric scaled, had large impact on exposure with exposure decreasing with higher weight. At the weight extremes 37-147 kg, the fold change in AUC was 1.61 and 0.57 from the average 70 kg subject.

Figure 2. Covariate Effects on Steady-State Surufatinib AUC



For all covariate scenarios, all other covariates were maintained at values for the reference subject (70-kg Asian male subject). Numbers in the right-hand panel represent the median [95% CI] ratio. Simulation assumed a 300 mg QD surufatinib.
AUC = area under the concentration-time curve; CI = confidence interval; Non-Asian = race other than Asian; QD = once daily.

PBPK modelling

A PBPK model including a mechanistic absorption model (Simcyp ADAM model) for description of drug absorption and gut metabolism, was developed for surufatinib. The final PBPK model was a minimal model with a single adjustment compartment.

Figure 3. Minimal physiologically based pharmacokinetic model with single adjusting compartment (SAC)

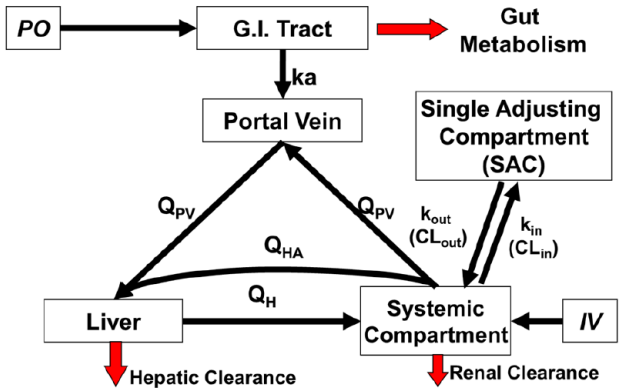


Figure 3. Minimal physiologically based pharmacokinetic model with single adjusting compartment (SAC).
Q_H, Q_{PV}, and Q_{HA} are blood flows in the liver, portal vein, and hepatic artery, respectively; k_{in} and k_{out} are first order rate constants which act on the masses of drug within the systemic compartment and the SAC respectively; PO is oral dosing route; fa is the fraction absorbed from the gut and ka is the associated first order absorption rate constant.

The PBPK model assumed high passive permeability (Fa 0.97) based on fecal recovery of unchanged drug, with limited the P-gp mediated contribution of intestinal uptake. The model could capture clinical observations from single dose and multiple dose studies and from healthy subjects and patients. Surufatinib is a time-dependent inhibitor of CYP3A4, which is also the main route of metabolism (70%). To simulate auto-inhibition, KI and kinact values for TDI of CYP3A4/5 in vitro were incorporated in the PBPK model. To verify that the model could capture the effect of TDI, predicted exposures were compared to clinically observations after repeat dosing of surufatinib over an 8-fold dose range in cancer patients.

Figure 4. Linear (left) and log-linear (right) stimulated (lines) and individual observed plasma concentration-time profiles of surufatinib following multiple doses of surufatinib (300 mg) to cancer patients

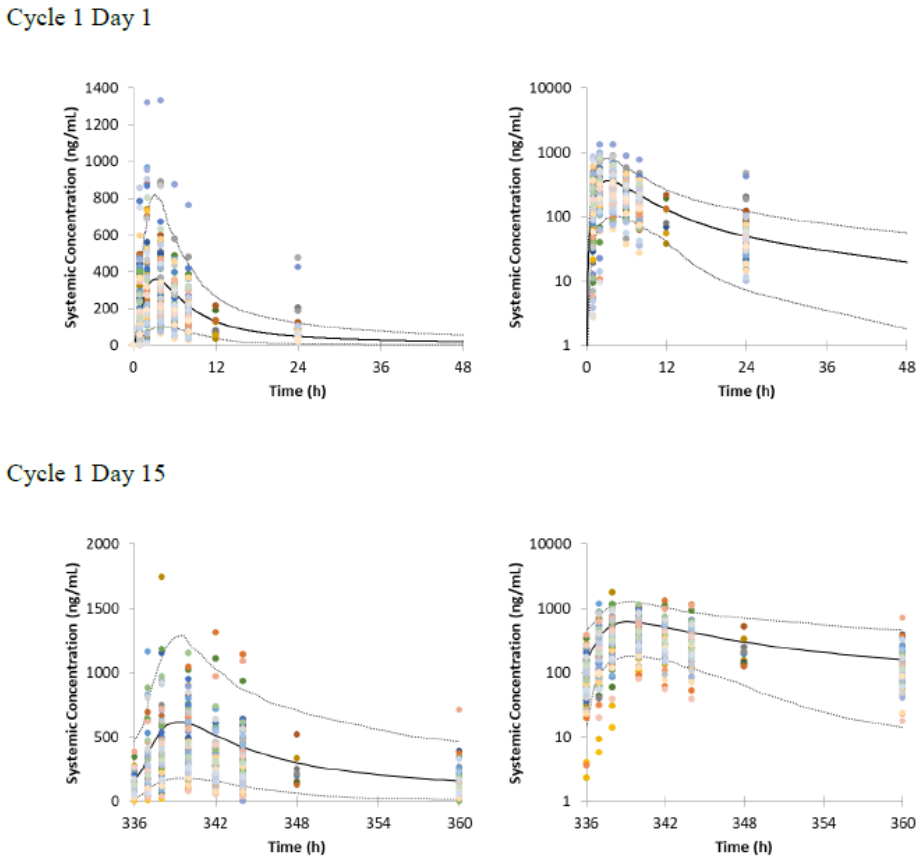
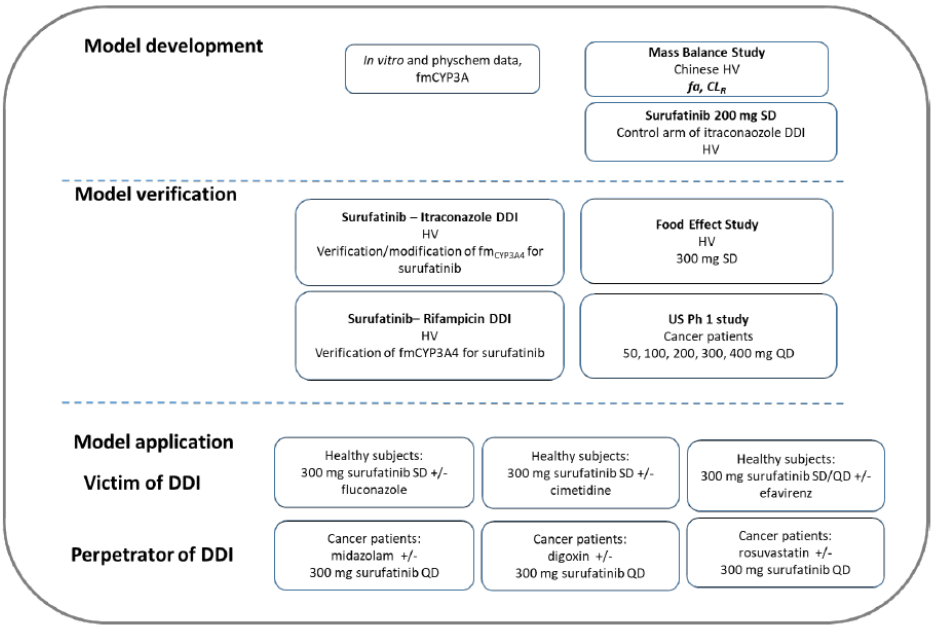


Figure 21. Linear (left) and log-linear (right) simulated (lines) and individual observed (circles; Clinical Study 2015-012-00US1) plasma concentration-time profiles of surufatinib following multiple doses of surufatinib (300 mg) to cancer patients.
The solid line is the mean data for the simulated population and the dashed lines are the 5th and 95th percentiles (n = 237) [source data: hum-2015-us1-mad-300mg-c1d1.xlsx, hum-2015-us1-mad-300mg-c1d15.xlsx].

The clinical data from a DDI study with itraconazole, a strong inhibitor of CYP3A4 and P-gp, was well captured by the PBPK model with a slight overprediction of surufatinib exposure with and without itraconazole. Simulation of the effects of moderate and weak inhibitors of CYP3A4 on surufatinib exposure are accepted for SmPC recommendations. The clinical data from a DDI study with rifampin, a strong inducer of CYP3A4, was slightly overpredicted by the model but the magnitude of effect was well captured. The simulation of induction is not considered acceptable for SmPC recommendations since the PBPK platform is not considered qualified for induction according to the PBPK Guideline. However, surufatinib is predominately metabolised via CYP3A4 and the simulations with moderate inducer efavirenz was used to warn prescribers against concomitant use of moderate CYP3A inducers, which is accepted. The model was also used to simulate DDI with fluconazole (moderate CYP3A inhibitor), cimetidine (weak CYP3A4 inhibitor) or efavirenz (moderate CYP3A inducer) in a healthy virtual population and with midazolam (CYP3A4 substrate), digoxin (P-gp substrate) or rosuvastatin (BCRP substrate) in a virtual cancer patient population. Simulations of surufatinib inhibition of CYP3A4, P-gp and BCRP substrates are not accepted for SmPC recommendations since the PBPK platform is not considered adequately qualified for high impact use according to the PBPK Guideline. An ongoing study

is investigating these interactions. The clinical results will be expected to guide any recommendations in the SmPC regarding the inhibitory effects of surufatinib.

Figure 5. Schematic showing the key PBPK modelling steps and components of each clinical study used in model building and verification.



Absorption

Mass balance data suggest an almost complete absorption of surufatinib. Tmax was 3 hours in healthy subjects after administration of a single 300 mg surufatinib suspension. In a patient study involving 300 mg as capsules, Tmax was approximately 2 hours, which is the reported Tmax in the SmPC. If administered once daily, steady state is reported to be achieved after 7 days with an accumulation ratio of 1.7.

Patient Cmax in NCA study 2009-012-00CH1 is comparable to Cmax in the integrated popPK multiple dose patient analysis.

Patients had 1.7-fold higher Cmax and 1.3-fold higher AUC0-24 than healthy subjects, indicating that the disease state affects the PK of surufatinib.

The solubility of surufatinib is pH dependent. An absolute bioavailability study in humans is not available. *In vitro* data indicate that surufatinib has moderate passive permeability across cell membranes.

Some important popPK derived PK parameters in the target population is found in Table 2.

Table 2. Summary of Dose-Normalized Surufatinib Model-Predicted Exposures to 300 mg Surufatinib, CL/F and Vss/F

Exposure/PK Parameter	N	Mean (%CV)	Geometric Mean (Geometric %CV)	Median [Maximum, Minimum]
AUCss (ng•h/mL)/300 mg	385	5092.6925 (61.31)	4361.2278 (61.02)	4333.1311 [619.746, 24910.19]
C_{maxss} (ng/mL)/300 mg	385	480.0033 (60.15)	410.6048 (61.31)	408.308 [56.158, 1950.74]
C_{minss} (ng/mL)/300 mg	385	105.2344 (69.77)	86.7335 (69.33)	85.022 [11.566, 553.84]
CL/F (L/h)	385	76.1869 (55.27)	66.93 (54.8)	69.154 [12.0433, 332.72]
Vss/F (L)	385	1852.9005 (48.94)	1666.3545 (49.05)	1689.32 [359.3751, 7947.3]

Geometric mean and geometric %CV were calculated as exp(mean(log(x))) and sqrt(exp(sd(log(x))^2)-1)*100, respectively, where sqrt is the square root function and sd is standard deviation.
AUCss = steady-state area under the plasma concentration-time curve; CL/F = apparent clearance; C_{maxss} = steady-state maximum plasma concentration; C_{minss} = steady-state minimum plasma concentration; CV = coefficient of variation; N = number of subjects; PK = pharmacokinetic; Vss/F = apparent total volume of distribution.

Distribution

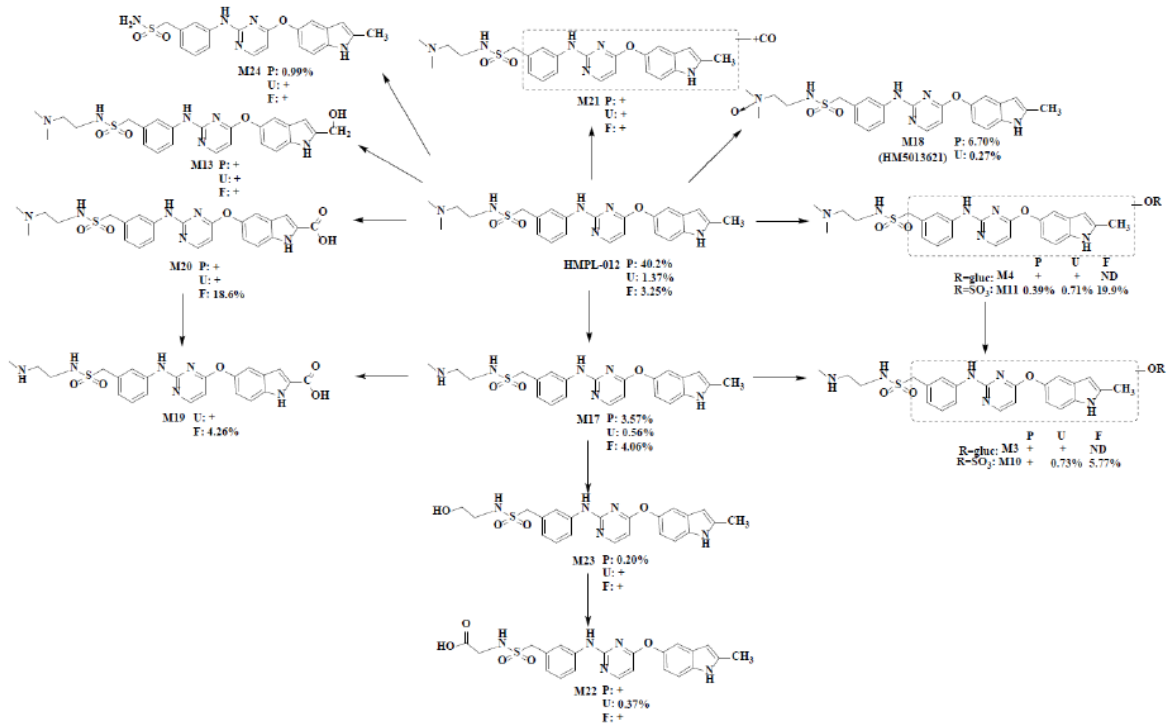
In the mass balance study, for those whole blood samples where radioactivity was detectable, the ratio of total radioactivity in whole blood to plasma was <1 and fell between 0.531 and 0.675. This suggested that total radioactivity was not significantly bound to blood cells. The apparent volume of distribution (Vd) is large, estimated to be 1831 L, suggesting a high degree of extravascular distribution.

Elimination

CYP3A4 is considered to be the primary metabolising enzyme. In vitro, the CYP3A4 was the predominant metabolising enzyme contributing with approximately 87%.

The metabolism of surufatinib is complex, as depicted in the figure below:

Figure 6. Proposed Metabolic Pathways of Surufatinib in Human (study 2017-012-00CH1)



+=only detected by LC-MS/MS; %AUC=percentage of area under the total radioactivity-time curve; %Dose=percentage of radioactive dose; F=feces (%Dose); gluc=glucuronide (C6H8O6); LC-MS/MS=liquid chromatography with tandem mass spectrometry; ND=not detected; P=plasma (%AUC); U=urine; (%Dose).
Source: Report RPT00335, Figure 46

Excretion of surufatinib is predominantly via the hepato-biliary route, the amount of unchanged substance was only 1.37% of the administered dose in the mass balance study. No metabolites accounting for >10% of the total exposure were found in plasma. The elimination half-life is approximately 19 hours.

In the integrated pop PK analysis, the apparent clearance (CL/F) of surufatinib was about 62 L/h at steady state following 300 mg QD dosing.

Dose proportionality and time dependencies

A power model of dose proportionality based on PK data from US patients indicated that the increase in exposure between doses of 50 and 400 mg was proportional to the increase in dose (Table 3). The 95% confidence interval (CI) of the slope estimate for surufatinib AUC0-24, AUCtau, and Cmax included the value of 1, and the slope itself was contained within 0.8 and 1.2, suggesting dose proportionality in both single dose and multiple dose in the dose range 50-400 mg.

Table 3. Dose Proportionality Evaluation of Oral Surufatinib (study 2015-012-00US1)

Visit	Dependent	Slope	Standard Error	Denom_DF	$T_{critical}$	95% CI (Lower)	95% CI (Upper)
Cycle 1 day1	LnC_{max}	0.849	0.145	103	1.98	0.560	1.14
	$LnAUC_{0-24}$	0.989	0.132	91	1.99	0.727	1.25
Cycle 1 day 15	LnC_{max}	0.882	0.146	92	1.99	0.593	1.17
	$LnAUC_{tau}$	1.05	0.139	88	1.99	0.772	1.32
Cycle 2 day1	LnC_{max}	0.843	0.156	36	2.03	0.525	1.16
	$LnAUC_{tau}$	0.986	0.139	32	2.04	0.703	1.27

AUC_{0-24}=area under the plasma concentration-time curve from time 0 to 24 hours postdose; AUC_{tau}=area under the plasma concentration-time curve for the dosing interval; CI=confidence interval; C_{max}=maximum plasma concentration; Denom_DF=denominator degrees of freedom; Ln=natural logarithm.

Note: $T_{critical}=t_{(\alpha-1),df}$ (where α is the statistical significance level and df is degrees of freedom).

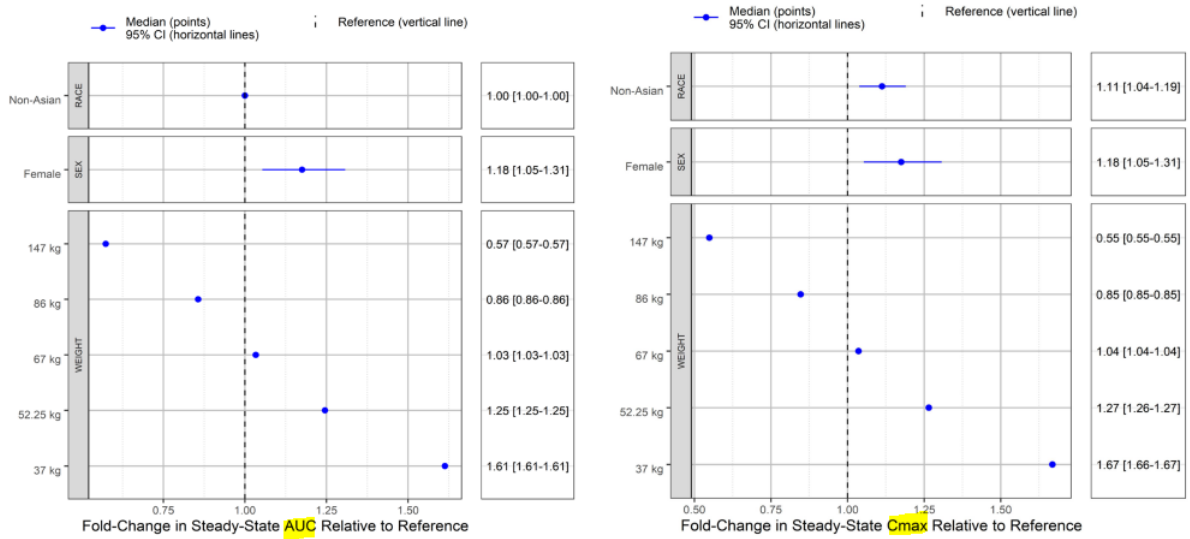
Source: PK Analysis Report, Table 10-12

Surufatinib may cause auto-inhibition of CYP3A4, which can result in a time dependent change in the clearance of surufatinib.

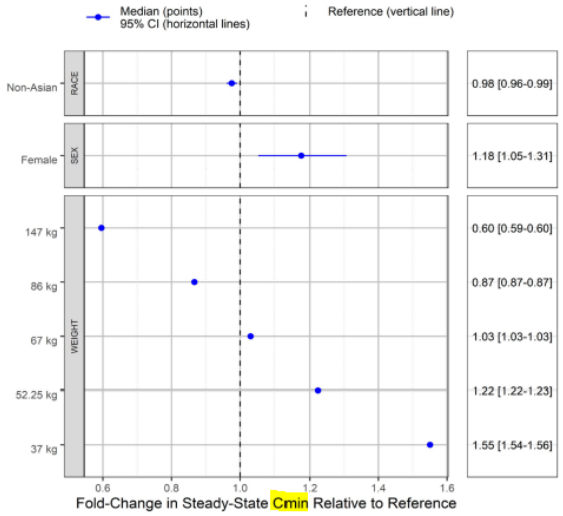
Special populations

In pop PK study HMPI-PMX-SURU-2293, the objectives were to develop a pop PK model of surufatinib to characterize the PK of surufatinib and to assess sources of PK variability. In this model, data from the two phase 3 studies are included. The effect of race, gender, and weight is depicted in **Figure 7**.

Figure 7. Forest Plots of the Effects of Demographic Factors on the Exposure of Surufatinib (Study HMPI-PMX-SURU-2293)



(Continued)



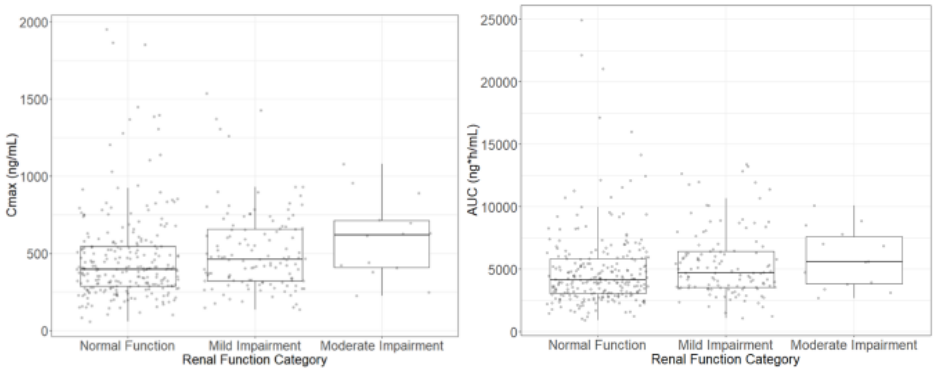
AUC=area under the plasma concentration-time curve; CI=confidence interval; C_{max}=maximum plasma concentration; non-Asian=race other than Asian.
Notes: The forest plots depict the median ratios (95% CI) of steady state exposures of surufatinib at the covariate values illustrated relative to the corresponding values in a reference patient (Asian male patient weighing 70 kg). The 95% CI was defined as the middle 95% of the ratios (ie, the ratios spanning the 2.5th and 97.5th percentiles). For body weight, the covariate effects are presented for the minimum value; 10th, 50th, and 90th percentiles, and the maximum value of body weight in the analysis dataset.
Source: Study HMPI-PMX-SURU-2293, Figure 12, Figure 13, and Figure 14

Impaired renal function

Based on pop PK assessment, mild renal impairment does not seem to affect the exposure of surufatinib (Figure 8), and dose adjustment is thus not necessary. Data on subjects with moderate impairment are sparse (n=14) and this is reflected in the SmPC.

According to the PK documentation, a phase 1 study assessing the effect of moderate renal impairment on the pharmacokinetics of surufatinib is ongoing and does not contribute data to this application.

Figure 8. Boxplots of Surufatinib Cmax and AUC stratified by Renal Function Category (Study HMPI-PMX-SURU-2293)

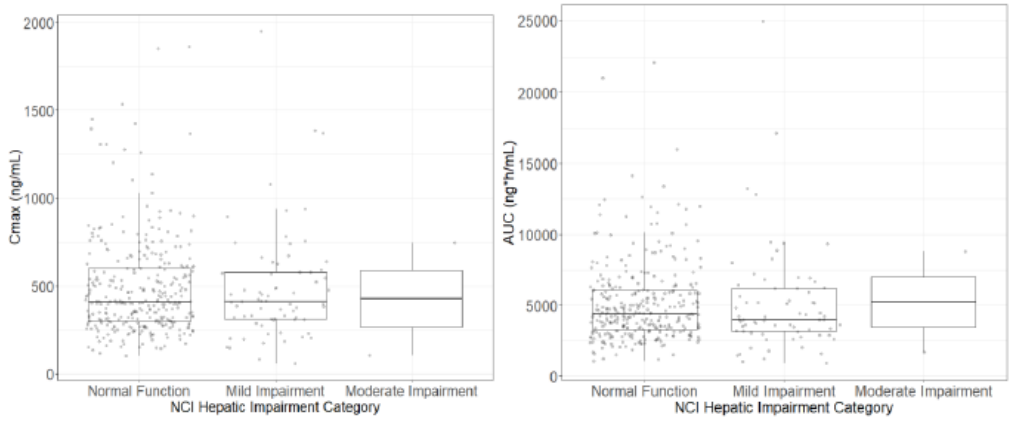


AUC=area under the plasma concentration-time curve; C_{max}=maximum plasma concentration; IQR=interquartile range.
Notes: The solid line is the median. The ends of the "box" are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5×IQR of the lower quartile and the highest value still within 1.5×IQR of the upper quartile. The circles are observed data.
Source: Study HMPI-PMX-SURU-2293, Figure 16 and Appendix 1.2.15

Impaired hepatic function

Based on pop PK assessment, mild hepatic impairment does not seem to affect the exposure of surufatinib (Figure 9), and dose adjustment is thus not necessary. Data on the impact of moderate impairment is very sparse (n=2), and this is reflected in the SmPC. According to the PK documentation, a phase 1 study assessing the effect of moderate hepatic impairment on the pharmacokinetics of surufatinib is ongoing and does not contribute data to this application. Data on severe hepatic impairment will not be generated, and the product is not recommended in this population.

Figure 9. Boxplots of Surufatinib Cmax and AUC Stratified by Hepatic Function Category (Study HMPI-PMX-SURU-2293)



AUC=area under the plasma concentration-time curve; C_{max}=maximum plasma concentration; IQR=interquartile range; NCI=National Cancer Institute.
Notes: The solid line is the median. The ends of the "box" are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5×IQR of the lower quartile and the highest value still within 1.5×IQR of the upper quartile. The circles are observed data.
Source: Study HMPI-PMX-SURU-2293, Figure 17 and Appendix 1.2.15

Gender

Gender is considered not to be a clinically important covariate (Figure 7). The overall exposure is estimated to be slightly (18%) higher in females than in males.

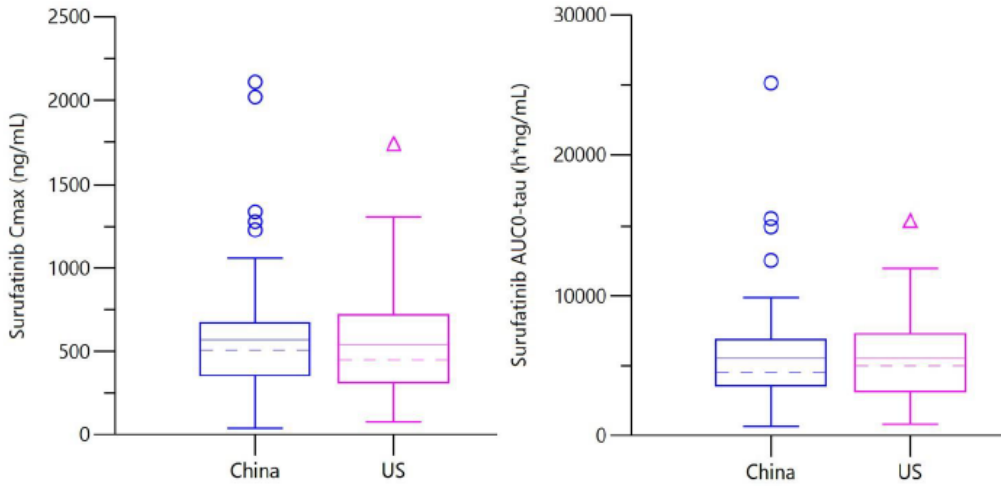
Weight

As depicted in Figure 7, a clear relationship between weight and exposure has been demonstrated. Within the 10th (52 kg) and 90th (86 kg) percentiles of weight, the exposure is estimated to be approximately 25% higher and 15% lower, respectively, compared to a 70 kg reference subject. This weight effect does not warrant any dose adjustments and this also applies to more extreme body weights (37-147 kg).

Race

Race does not seem to influence PK of surufatinib. There was no observed difference in surufatinib PK between the clinical studies conducted in the US and those conducted in China.

Figure 10. Box Plots of Surufatinib Cmax and AUC Following Multiple Doses of Surufatinib 300 mg in Patients with Cancer from China and the United States



AUC_{tau}=area under the plasma concentration-time curve for the dosing interval; C_{max}=maximum plasma concentration; IQR=interquartile range.

Notes: The dashed line is the median; the solid line is the arithmetic mean. The ends of the "box" are the 25th and 75th percentiles. The whiskers show the lowest data value still within 1.5×IQR of the lower quartile and the highest value still within 1.5×IQR of the upper quartile. The open circles or triangles are outliers.

Source: Pharmacokinetic Memorandum: Pharmacokinetics of Surufatinib in Healthy Subjects and Patients with Cancer, Figure 4

Age

Age (range: 19 to 85 years) was not identified as a meaningful covariate on the PK of surufatinib based on PopPK analysis. The number of elderly subjects in the different age categories are shown in Table below.

Table 4. Number of Elderly Subjects by Age Group

	Age (No. of Elderly Subjects / Total Number in Study (% of Study)		
Study	65 to 74 years	75 to 84 years	>85 years
2014-012-00CH1	13/81 (16%)	0/81 (0%)	0/81 (0%)
2015-012-00CH3	10/89 (11.2%)	1/89 (1.1%)	0/89 (0%)
2015-012-00CH4	12/110 (10.9%)	0/110 (0%)	0/110 (0%)
2015-012-00US1	38/105 (36.2%)	4/105 (3.8%)	1/105 (1%)
Total	73/385 (19%)	5/385 (1.3%)	1/385 (0.3%)

No.=number.

Genetic differences

The effects of genetic polymorphism on the PK of surufatinib have not been evaluated. Surufatinib is metabolized primarily by CYP3A4 and, to a minor extent, by CYP3A5, CYP2D6, and CYP2C9. To date, no major pharmacogenetic differences in CYP3A4 variants have been identified.

Pharmacokinetic interaction studies

The PBPK model was able to predict the observed data obtained from the clinical itraconazole and rifampin studies with high accuracy. Surufatinib is a substrate of CYP3A4, CYP3A5, CYP2D6, and CYP2C9. Coadministration with a strong CYP3A inhibitor (itraconazole) only led to a 2-fold increase in surufatinib exposure, indicating significant elimination pathways other than CYP3A4. In aqueous media, surufatinib exhibits pH dependent solubility and acid-reducing agents could affect the solubility and absorption of surufatinib. However, coadministration of surufatinib and rabeprazole (a PPI) only slightly increased the exposure of surufatinib (both AUC and Cmax < 15%) and had no effect on surufatinib t½. Coadministration of surufatinib and rifampin (strong CYP3A inducer) decreased the exposure of surufatinib by 2.6-fold for Cmax and 3.9-fold for AUC and reduced the surufatinib t½ significantly.

Pharmacokinetics using human biomaterials

In vitro, surufatinib was a substrate for P-gp transport and CYP3A metabolism.

In vitro, surufatinib did not induce or have reversible inhibitory effects on CYP enzymes, but did have a strong time-dependent inhibitory effect on CYP3A4/5, which may increase the in vivo exposure of concomitant drugs that have CYP3A4/5-mediated metabolism. In vitro, surufatinib also inhibited P-gp and BCRP, which may affect the oral absorption of coadministered drugs that are P-gp and/or BCRP substrates. This will be evaluated in a clinical study.

In vitro, it has been shown that, at therapeutically relevant concentrations, surufatinib is not an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, or MATE2-K and thus is unlikely to affect clearance of substrates of these transporters.

Pharmacodynamics

Surufatinib is a novel small molecule kinase inhibitor with antitumor activity targeting two different tumorigenic mechanisms. By selectively inhibiting VEGFR and FGFR-1, surufatinib suppresses tumor angiogenesis, which leads to tumor deprivation of nutrients and oxygen. Surufatinib also suppresses tumor immune evasion via inhibition of CSF1R activity.

No specific pharmacodynamic (PD) biomarker was defined and reported.

Assessment of an exposure-efficacy relationship was conducted using PFS and ORR as efficacy parameters. For assessment of an exposure-safety relationship, any grade and grade 3 or higher (grade ≥3) occurrence of hepatic disorder, proteinuria, hypertension, thyroid dysfunction, hemorrhage, and acute renal failure.

Primary and Secondary pharmacology

No specific PD endpoints or biomarkers were defined and reported. Accordingly, no PD biomarkers are proposed for monitoring of effect.

Concentration QTc modelling

Sparse sampled post-baseline ΔQTc-concentration pairs from 94 subjects from Study 2015-012-00US1 were included in the concentration-QTc analysis (40% of all available concentration-ΔQTcF pairs were excluded leaving 231 valid observations). The final C-QTcF model for surufatinib was a linear model with an intercept and effects of surufatinib concentration and baseline QTcF on ΔQTcF, with random effects on the intercept and the ΔQTcF-concentration slope. The model was evaluated by goodness-of-fit plots. The VPC showed some fluctuation in ΔQTc at lower concentrations not captured by the model

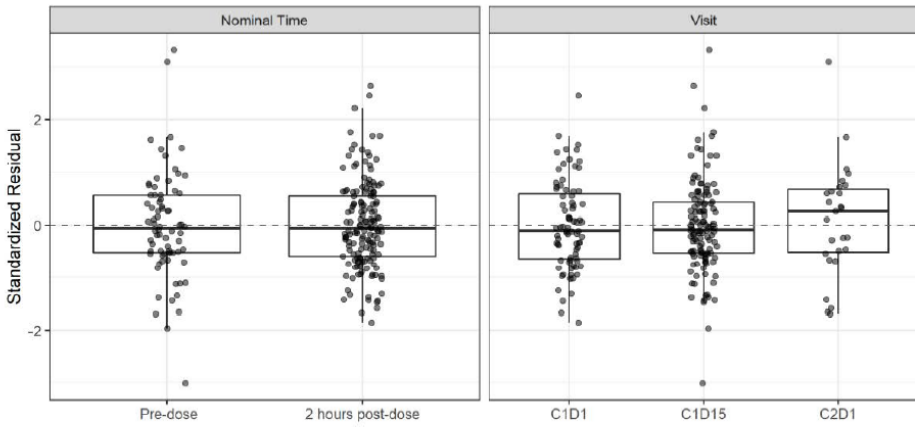
but there was no indication of a positive relation between concentration and ΔQTcF. The ECGs were centrally analysed by a semi-automatic mode of ECG analysis.

Table 5. Model Parameters Estimates for the Final C-QTc Model

Parameter	Estimate	SE	RSE%	95 CI%	p-value
Intercept (ms)	1.08	1.46	135	(-1.78, 3.94)	0.4586
Slope (ms per ng/mL)	-0.00493	0.00347	70.4	(-0.0117, 0.00188)	0.1569
Baseline QTcF Coefficient	-0.196	0.052	26.5	(-0.299, -0.0938)	0.0003
Intercept BSV SD (ms)	7.14	1.37	19.2	(4.94, 10.3)	
Slope BSV SD (ms per ng/mL)	0.00784	0.00657	83.8	(0.00232, 0.0265)	
Residual error SD (ms)	11.9	0.698	5.87	(10.6, 13.3)	

BSV = between-subject variability; C-QTc = concentration-corrected QT interval; CI = confidence interval; p-value = p-value based on Wald test; QTcF = corrected QT interval using Fridericia's method; RSE = relative standard error; SD = standard deviation; SE = standard error.

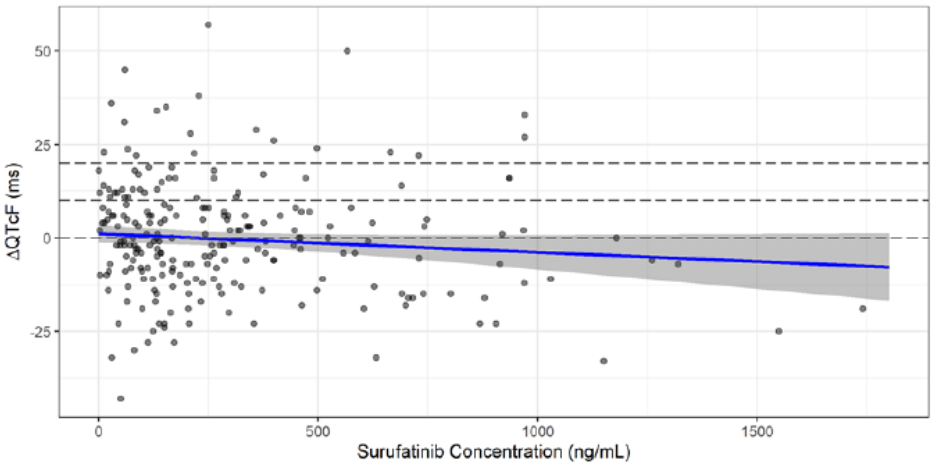
Figure 11. Final C-QTc Model: Standardized Residuals Versus Nominal Time and Study Visit



Closed circles represent individual data points. The black dashed line represents y = 0.
C-QTc = concentration-corrected QT interval; CmDn = Cycle m Day n.

The concentration-QTcF analysis, based on data from Study 2015-012-00US1, showed no statistically significant or clinically meaningful association between plasma concentrations of surufatinib and ΔQTcF (**Figure 12**). The predicted mean (90% CI) ΔQTcF for the geometric mean Cmax value of 456 ng/mL surufatinib at steady state following a dose of 300 mg QD was -1.17 (-3.36, 1.02) ms. The upper bounds of the 90% CI of the predicted mean ΔQTcF associated with 1 to 3 times the steady state geometric mean Cmax of 300 mg QD were all below 10 ms. In agreement with these findings, the results of the by-timepoint analysis showed that the maximum least-squares mean ΔQTcF observed in the dose-escalation part was 2.80 ms (90% CI: -3.43, 9.03) at predose on cycle 1 day 15, and in the dose-expansion part was -1.14 ms (90% CI: -3.85, 1.57) at 2-hour postdose on cycle 1 day 15.

Figure 12. Model-Predicted Relationship Between ΔQTcF and Surufatinib Concentration (Study HMPI-PMX-SURU-2293)



CI=confidence interval; ΔQTcF=change from baseline QTcF; QTcF=heart rate-corrected QT interval calculated using Fridericia's formula.
Notes: Closed circles represent individual observations. Blue line represents model prediction. Gray-shaded region represents the 90% CI of the model prediction. Dashed lines are reference lines for ΔQTcF=0, 10, and 20 ms.
Source: HMPI-PMX-SURU-2293, concentration-QTc analysis, Figure 43

Exposure-response analyses

Safety endpoints (occurrence of selected AEs) and the efficacy endpoint of objective response were treated as binary variables. The efficacy endpoint of progression free survival was treated as a time-to-event variable. Surufatinib exposure metrics investigated were AUC, Cmax, and Cmin at steady-state.

Tabular or graphical summaries of AEs by surufatinib exposure quantiles were generated for binary safety endpoints. The relationship between surufatinib steady-state exposure and the probability of experiencing AEs were evaluated using univariate logistic regression analysis. For efficacy, separate analyses were performed for subjects with epNET and pNET. Univariate logistic regression models were used for ORR and Cox regression models for PFS.

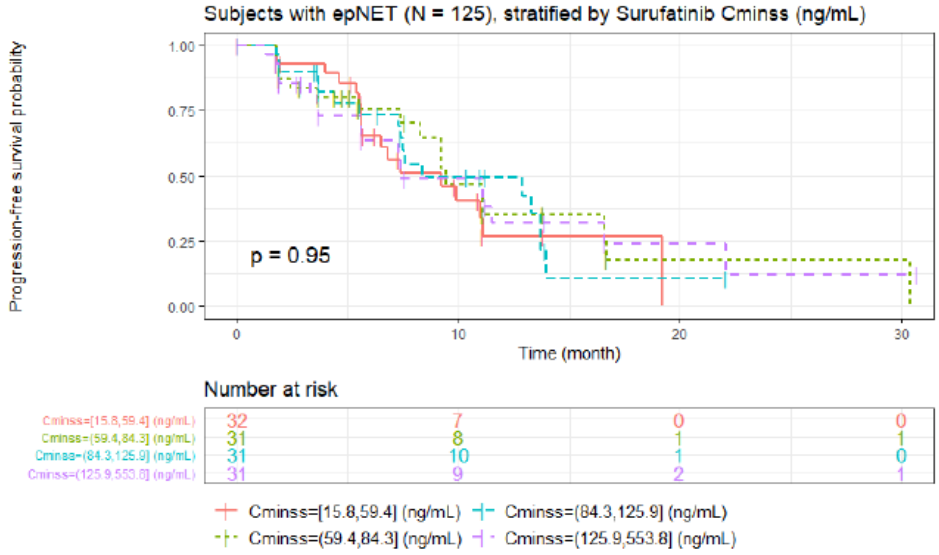
Exposure-efficacy relationships

The objectives were to explore the relationship between surufatinib exposure and efficacy (PFS and ORR) in patients with advanced pNET and patients with epNET.

Separate efficacy E-R analyses for the primary efficacy endpoint of PFS and the secondary efficacy endpoint of ORR based on investigator assessment were performed for patients with pNET using data from SANET-p and for patients with epNET using data from SANET-ep. Patients with pNET and epNET from Study 2015-012-00US1 were also included in the respective efficacy E-R analyses. All patients included in the efficacy E-R analyses received a starting dose of 300 mg QD surufatinib. The exposure measure selected for all efficacy E-R models was $C_{min,ss}$.

As for the **epNET subset**, no PFS or ORR E-R relationship was found (Figure 13 and Table 6).

Figure 13. Kaplan-Meier Plot of PPS in the epNET Subset Stratified by Surufatinib $C_{min,55}$ Quartiles



$C_{min,ss}$=minimum plasma concentration at steady state; N=number of patients; PFS=progression-free survival; epNET=extrapancreatic neuroendocrine tumor.
Source: Study HMPI-PMX-SURU-2293, Figure 24

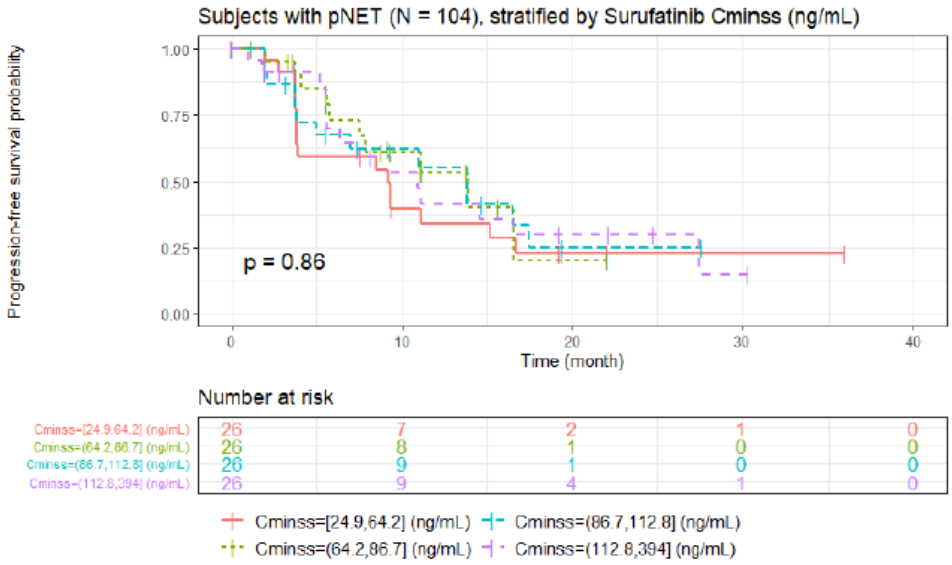
Table 6. Final E-R Model Parameter Estimates for ORR in Patients With epNET

Parameter	Estimate	RSE%	p-value	Odds Ratio (95% CI)
Intercept	0.10200	1247.6	0.9361	-
Surufatinib $C_{min,ss}$ (per ng/mL)	0.00392	76.3	0.1903	1.004 (0.99739, 1.0098)
Age (per year)	-0.05780	42.1	0.0175	0.9438 (0.89758, 0.98905)

CI=confidence interval; $C_{min,ss}$=minimum plasma concentration at steady state; E-R=exposure-response; epNET=extrapancreatic neuroendocrine tumor; ORR=objective response rate; RSE=relative standard error.
Source: Study HMPI-PMX-SURU-2293, Table 31

As for the **pNET subset**, no PFS E-R relationship was found (Figure 14) but for every 1 ng/mL increase in Cmin,ss the odds ratio of a patient experiencing objective response (ORR) increases by 0.8% (Table 8, the Applicant writes 0.08% which is considered a possible typo). In addition, the popPK model found a statistically significant effect of baseline ECOG score on PFS in patients with pNET with a baseline ECOG score of 1 associated with worse PFS (Table 7).

Figure 14. Kaplan-Meier Plot of PPS in the pNET Subset Stratified by Surufatinib Model-Predicted $C_{min,55}$ Quartiles (Study HMPI-PMX-SURU-2293)



$C_{min,ss}$=minimum concentration at steady state; N=number of patients; PFS=progression-free survival; pNET=pancreatic neuroendocrine tumor.
Source: Study HMPI-PMX-SURU-2293, Figure 26

Table 7. Final E-R Model Parameter Estimates for PFS in Patients With pNET (Study HMPI-PMX-SURU-2293)

Parameter	HR	95% CI	p-Value
Surufatinib $C_{min,ss}$ (per ng/mL)	0.9988	0.9951, 1.003	0.5398
Baseline ECOG score: 1	1.964	1.134, 3.402	0.0160

CI=confidence interval; $C_{min,ss}$=minimum concentration at steady state; ECOG=Eastern Cooperative Oncology Group; E-R=exposure-response; HR=hazard ratio; PFS=progression-free survival; pNET=pancreatic neuroendocrine tumor.
Source: Study HMPI-PMX-SURU-2293, Table 29

Table 8. Final E-R Model Parameter Estimates for ORR in Patients With pNET (Study HMPI-PMX-SURU-2293)

Parameter	Estimate	RSE%	p-Value	Odds Ratio (95% CI)
Intercept	-2.20000	21.2	<0.0001	-
Surufatinib $C_{min,ss}$ (per ng/mL)	0.00821	39.5	0.0113	1.008 (1.002, 1.0151)

CI=confidence interval; $C_{min,ss}$=minimum plasma concentration at steady state; E-R=exposure-response; ORR=objective response rate; pNET=pancreatic neuroendocrine tumor; RSE=relative standard error.
Source: Study HMPI-PMX-SURU-2293, Table 33

Exposure-safety relationships

The safety E-R analysis included 380 patients from 4 studies (2014-012-00CH1, 2015-012-00CH4 [SANET-ep], 2015-012-00CH3 [SANET-p], and 2015-012-00US1). Assigned surufatinib doses ranged from 50 to 400 mg QD. The analyses used AUCss, Cmax,ss, and Cmin,ss as exposure parameters. The safety endpoints that were investigated in this analysis were any grade and grade 3 or higher (grade

≥3) occurrence of the following adverse events (AEs) of special interest at any point during the study: Hepatic disorder, proteinuria, hypertension, thyroid dysfunction, hemorrhage, and acute renal failure.

The following AEs showed statistically significant E-R relationships with all surufatinib model-predicted steady state exposure measures (AUCss, Cmax,ss, and Cmin,ss, except as noted; the p-value for the most statistically significant [slope p<0.05] exposure measure is provided):

· Any grade acute renal failure (Cmax,ss p=0.0009)

· Any grade hepatic disorder (Cmax,ss p=0.0354; AUCss and Cmin,ss not statistically significant)

· Any grade thyroid dysfunction (AUCss p=0.0125)

· Grade ≥3 acute renal failure (AUCss p=0.0019)

· Grade ≥3 hepatic disorder (Cmax,ss p=0.0078)

· Grade ≥3 proteinuria (AUCss p=0.0201)

Discussion on clinical pharmacology

Surufatinib is a small molecule kinase inhibitor, which inhibits vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3; fibroblast growth factor receptor-1 (FGFR-1), and colony-stimulating factor-1 receptor (CSF1R). It has been developed for the treatment of adult patients with neuroendocrine tumours of extrapancreatic or pancreatic origin that are locally advanced or metastatic. Fifteen clinical studies with surufatinib have been completed (6 in healthy volunteers and 9 in patients with cancer). Of the 15 clinical studies, 11 were conducted in China and 4 were conducted in the US. The recommended dose is 300 mg orally once daily. Dose proportionality in both single dose and multiple dose has been demonstrated for Cmax and AUC in the dose range 50-400 mg. The dose regimen is considered acceptable.

Surufatinib was quantitated in human plasma by validated LC-MS/MS methods. Population PK analyses was conducted using only data from patients. Data from healthy subjects was not included. The effect of weight on CL and V was allometric scaled with standard fixed exponents. Race and sex were significant covariates but the effects were not considered clinically relevant. Weight had large impact on exposure. A PBPK model was developed for surufatinib and used to simulate DDI. The final PBPK model could capture clinical observations from single dose and multiple dose studies, from healthy subjects and patients and data from two clinical DDI studies. However, a question to the qualification of the model remains and a Fa value of 0.97 was used in the model and this needs further justification. The PBPK model cannot be used to waive all clinical DDI studies with surufatinib since the model is not sufficiently qualified. Clinical results of ongoing interaction studies are expected to guide the recommendations in the SmPC regarding the inhibitory effects of surufatinib.

In a patient study involving 300 mg as capsules, Tmax was approximately 2 hours, which is the reported Tmax in the SmPC. If administered once daily, steady state is reported to be achieved after 7 days with an accumulation ratio of 1.7. The apparent volume of distribution (Vd) is large, estimated to be 1831 L, suggesting a high degree of extravascular distribution.

Absolute bioavailability of surufatinib has not been determined in humans.

CYP3A4 is considered to be the primary metabolising enzyme. In vitro, the CYP3A4 was the predominant metabolising enzyme contributing with approximately 87%. However, a question to the biotransformation pathway still remains. Genetic differences in CYP3A are not expected to influence the overall metabolism of surufatinib.

Excretion of surufatinib is predominantly via the hepato-biliary route, the amount of unchanged substance was only 1.37% of the administered dose in the mass balance study. No metabolites with >10% exposure were found in plasma. The elimination half-life is approximately 19 hours.

In the integrated pop PK analysis, the apparent clearance (CL/F) of surufatinib was about 62 L/h at steady state following 300 mg QD dosing. Due to auto-inhibition of CYP3A4 by surufatinib, a time dependent clearance has been reported.

The estimated inter-individual variability in clearance and exposure parameters ranges from 55-69%.

As to special populations, body weight and gender were identified as statistically significant covariates. However, the impact of these covariates is not considered clinically relevant, and dose adjustment is not necessary for body weight or gender. Age, race, and mild renal and hepatic impairment do not seem to influence the exposure of surufatinib. Two phase 1 studies assessing the effect of moderate renal impairment and moderate hepatic impairment on the pharmacokinetics of surufatinib are ongoing.

Surufatinib is a substrate of CYP3A4, CYP3A5, CYP2D6, and CYP2C9. Coadministration with a strong CYP3A inhibitor (itraconazole) only led to a 2-fold increase in surufatinib exposure, indicating significant elimination pathways other than CYP3A4. In aqueous media, surufatinib exhibits pH dependent solubility and acid-reducing agents could affect the solubility and absorption of surufatinib. However, coadministration of surufatinib and rabeprazole (a PPI) only slightly increased the exposure of surufatinib (both AUC and Cmax < 15%) and had no effect on surufatinib t½. Coadministration of surufatinib and rifampin (strong CYP3A inducer) decreased the exposure of surufatinib by 2.6-fold for Cmax and 3.9-fold for AUC and reduced the surufatinib t½ significantly. Surufatinib may be a clinically relevant inhibitor of OATP1B1 and OATP1B3 and this issue is not adequately elucidated.

No specific pharmacodynamic (PD) biomarker was defined and reported.

In a concentration-QTcF analysis on data from patients with advanced solid tumors, no evidence of QTc prolongation at clinically relevant surufatinib concentrations was found.

The exposure-efficacy analyses used $C_{min,ss}$ as exposure parameter and PFS and ORR as efficacy parameters. Separate analyses for pNET and epNET were conducted. As for the epNET subset, no PFS or ORR E-R relationship was found. As for the pNET subset, no PFS E-R relationship was found but for every 1 ng/mL increase in $C_{min,ss}$ the odds ratio of a patient experiencing objective response (ORR) increases by 0.8%. In addition, the popPK model found a statistically significant effect of baseline ECOG score on PFS in patients with pNET with a baseline ECOG score of 1 associated with worse PFS.

The exposure-safety analyses used AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$ as exposure parameters and the six selected AESIs as safety parameters. For several of the evaluated AESIs, statistically significant and clinically relevant exposure-safety relationships were reported.

Conclusions on clinical pharmacology

The clinical pharmacology package is comprehensive and relevant studies on renal and hepatic impairment are ongoing. Considering the nature of the product (kinase inhibitor), the pharmacology package is considered adequate and the proposed dosing of surufatinib seems appropriate, including in the special populations evaluated. No major objections were identified with respect to the clinical pharmacology. A number of PK/PD questions need to be addressed, though.

Clinical efficacy

Data from two pivotal phase 3 studies, along with data from a phase 1/1b study conducted in Western patients form the basis to support the marketing authorisation application (MAA) of surufatinib as treatment for advanced neuroendocrine tumours (NETs). One of the phase 3 studies was conducted in patients with NETs of extrapancreatic origin (epNETs), study 2015-012-00CH4 (**SANET-ep**), and the other one in patients with NETs of pancreatic origin (pNETs), study 2015-012-00CH3 (**SANET-p**). An additional study (2015-012-00US1, conducted with US patients) provides supportive efficacy data. Additional details regarding the pivotal efficacy clinical studies are presented in Table 9.

Table 9. Pivotal phase III trials of surufatinib in patients with neuroendocrine tumours.

Study Number Registration Study Type	Study Objective(s)	Study Design Treatment Arm(s) and Dose	Key Inclusion Criteria	Patient Population Sample Size Age (Years) Gender	Study Status
2015-012-00CH3 (SANET-p; NCT02589821) Phase 3	Primary: PFS Secondary: ORR, DCR, TTR, DoR, OS, safety, and tolerability	Randomized, double-blind, placebo-controlled, multicenter Surufatinib versus Placebo Oral surufatinib 300 mg QD	Histopathologically diagnosed with low- or intermediate-grade (G1 or G2) or advanced (unresectable locally advanced or distant metastatic) pNET Experienced PD after patient received ≤2 types of systemic antitumor drug treatment regimens	Advanced pNET 172 patients Mean Age: 49.9 years M/F: 51.2%/48.8%	Double-blind phase Completed; study stopped per IDMC evaluation after interim analysis showed superior efficacy Open-label phase ongoing
2015-012-00CH4 (SANET-ep NCT02588170) Phase 3	Primary: PFS Secondary: ORR, DCR, TTR, DoR, OS, safety, and tolerability	Randomized, double-blind, placebo-controlled, multicenter Surufatinib versus Placebo Oral surufatinib 300 mg QD	Histopathologically diagnosed with low- or intermediate-grade (G1 or G2) or advanced (unresectable locally advanced or distant metastatic) epNET Experienced PD after patient received ≤2 types of systemic antitumor drug treatment regimens	Advanced epNET 198 patients Mean Age: 52.5 years M/F: 54.5%/45.5%	Double-blind phase Completed; study stopped per IDMC evaluation after interim analysis showed superior efficacy Open-label phase ongoing

DCR=disease control rate; DoR=duration of response; epNET=extrapancreatic neuroendocrine tumor; MTD=maximum tolerated dose; NCT=national clinical trial; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; pNET=pancreatic neuroendocrine tumor; RP2D=recommended phase 2 dose; TTR=time to response; vs.=versus.

Extrapolation of the results to European population is considered problematic. The external validity of trials SANET-ep and SANET-p is unavoidably compromised due to differences in patient population enrolled, differences in disease characteristics such as tumour types represented in SANET-ep trial, and particularly treatment practices and available therapeutic options as compared to European population. In addition, baseline diagnostics and response assessment methods do not correspond to current clinical practice in the EU.

There is very limited data available in pretreated (2L+) patient population who would have received relevant first line treatments according to European treatment standards, and thus clinical benefit needs to be assessed in this population. The possible place of surufatinib in current treatment algorithms needs to be established.

At the presubmission meeting, the rapporteurs further stated that since surufatinib had not been compared to standard-of-care treatment, the applicant needed to justify how surufatinib compares to

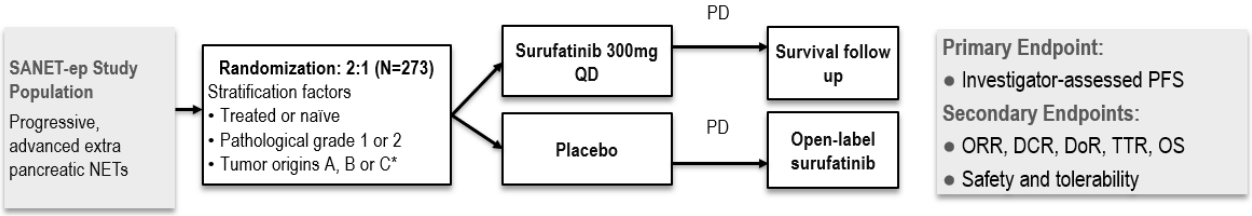
the other available treatment choices for the same patient population. In responses to D120 LoQ, this issue was not fulfilled: overall, it is not considered that surufatinib compares favourably against other treatment choices for similar patient populations.

Main studies

2015-012-00CH4 (SANET-ep)

Study 2015-012-00CH4 (SANET-ep) is a randomized, double-blind, placebo-controlled, multicentre, phase 3 clinical study to assess the efficacy and safety of surufatinib monotherapy in patients with advanced epNETs. An overview of the study design is provided in Figure 15.

Figure 15. Study design of SANET-ep



*Primary tumor lesion site A (jejunum, ileum, duodenum, thymus, and cecum) or B (lung, stomach, liver, appendix, colon, and rectum), or C (other or unknown origins)

The primary endpoint is PFS as determined by the investigator in accordance with Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1). Secondary endpoints included ORR, DCR, TTR, DoR, OS, and safety. As a supportive prespecified analysis, PFS is also assessed by a BIIRC.

Crossover: In the double-blind phase, patients were to receive continuous drug treatment of either surufatinib or placebo, until progressive disease, intolerable toxicity, or other criteria for termination of study treatment specified in the protocol. After progressive disease, unblinding was allowed and patients in the placebo arm were allowed to cross over to open-label surufatinib if they continued to meet the eligibility criteria and signed the consent to continue in the open-label phase. Of note, the possibility of unblinding at PD and crossover to surufatinib for patients in the placebo arm was implemented as of Protocol V2, dated 02-NOV-2016.

Interim analysis: An interim analysis was to be conducted after 70% of the PFS events (127 events) as assessed by investigator had occurred. The study allowed for early termination for efficacy, at the recommendation of the IDMC, if the interim analysis showed that the surufatinib arm crossed the prespecified efficacy boundary for PFS (defined as a 2-sided p-value <0.015.

Tumour assessment: Imaging evaluation was done every 8 weeks (±3 days) for the first year and every 12 weeks (±3 days) thereafter.

Methods

Study Participants

The target population of the study is patients in the progressive disease period who have unresectable locally advanced or distant metastasis, low and intermediate grade (G1 or G2) extrapancreatic NETs, including but not limited to lung, thymic and gastrointestinal NETs (stomach, duodenal, liver, jejunal, ileal, colon, caecal, appendix, rectal) and NETs of unknown origin.

Main inclusion criteria:

Patients of ≥18 years of age, with histopathological diagnosis of low- or intermediate-grade (G1 or G2) advanced (unresectable locally advanced or distant metastatic) extrapancreatic NETs. For

gastrointestinal neuroendocrine tumors (GI-NETs), low-grade (G1) is defined as mitotic count of < 2/10 high power fields [HPF] and/or Ki-67 differentiation index of < 3%; intermediate-grade (G2) is defined as mitotic count of 2–20/10 high power fields [HPF] and/or Ki-67 differentiation index of 3–20%. If the mitotic count and Ki- 67 index of the same tumor tissue correspond to different grades, the higher grade shall prevail. For lung and thymic NETs, G1 is defined as mitotic count of < 2/10 high power fields [HPF], not accompanied by necrosis lesions; G2 is defined as mitotic count of 2–10/10 high power fields [HPF] and/or necrosis lesions. Refer to the GI-NET grading criteria for NETs of other origins or unknown origins. (based on the central pathology review results).

Patients who experience progressive disease after receiving ≤2 types of systemic anti-tumor drug treatment regimens, such as somatostatin analogues, interferon, PRRT (peptide receptor radionuclide therapy), mTOR inhibitor or chemotherapy (regardless of the chemotherapy drugs and number of chemotherapy [cycles], chemotherapy is deemed to be a drug treatment regimen); treatment-naïve advanced patients who cannot accept or refuse to accept the aforementioned treatments may also be enrolled.

Disease progression of tumor confirmed by imaging within 12 months before randomization.

Patients with measurable lesions (in accordance with the RECIST 1.1 criteria).

Adequate hematologic and end-organ function, as defined by laboratory results.

ECOG performance status of 0 or 1 and expected survival of more than 12 weeks.

Main exclusion criteria

- Have high-grade (G3) neuroendocrine carcinoma, adenocarcinoid tumors, islet cell carcinoma, goblet cell carcinoid, large cell neuroendocrine carcinoma and small cell carcinoma.
- Have pancreatic neuroendocrine tumors.
- Have functional NET and require the use of long-acting somatostatin analogues to control symptoms, such as insulinoma, gastrinoma, glucagonoma, somatostatinoma, ACTH tumor, VIP tumor, accompanied by carcinoid syndrome, Zollinger-Ellison syndrome or disease-specific active symptoms.
- Patients who have previously received anti-VEGF-/VEGFR-targeted drug treatment and experienced progressive disease during the treatment period.
- Routine urine test shows urine protein ≥ 2+ or 24-hour urine protein quantification test shows urine protein ≥ 1 g.
- Have hypertension that cannot be stably controlled by drugs, defined as: systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg.
- Have gastrointestinal diseases or conditions that may affect drug absorption or other conditions that may lead to gastrointestinal hemorrhage or perforation as determined by the investigator.
- Have a history or current condition of severe hemorrhage (internal hemorrhage > 30 ml within three months), coughing blood (> 5 ml of fresh blood within four weeks) or thromboembolic events within 12 months (including transient ischemic attack).
- Have clinically significant cardiovascular diseases.
- A QTc interval of ≥ 480 milliseconds (ms) as shown by electrocardiogram (ECG) examination.
- Suffered from other malignancies within the past five years, except for basal cell carcinoma or squamous cell carcinoma of the skin after radical surgery and cervical carcinoma in situ.

- Have received anti-tumor treatment within four weeks prior to the start of study treatment, including but not limited to chemotherapy, definitive radiation therapy, biological targeted therapy, immunotherapy, Traditional Chinese medicine anti-tumor treatment, interventional hepatic artery embolization, cryoablation or radiofrequency ablation of liver metastases.
- Have received palliative radiotherapy for a bone metastasis lesion within two weeks prior to the initiation of investigational treatment.
- Have any clinically significant active infections, including but not limited to HIV, HBV, HCV.
- Have undergone surgery (except for biopsy) within 28 days before the first administration of the study drug or have unhealed surgical incisions.
- Have brain metastases or spinal cord compression not treated by surgery and/or radiotherapy, or previously treated brain metastases or spinal cord compression without clinical imaging evidence of stable condition.
- Have toxicity from a previous anti-tumor treatment that does not return to grade 0 or 1 (except for hair loss).
- Participated in other drug clinical trials and received the corresponding investigational drug treatment within the past four weeks.
- Pregnant (positive pregnancy test before drug administration) or lactating women.
- Have any other diseases, metabolic abnormalities, physical examination abnormalities or laboratory test abnormalities which, based on the investigator's judgment, constitute reasons to suspect that the patient has a certain disease or condition that would make the patient unsuitable to take the study drug or affect the interpretation of the study results.

The clinical scenario of patients who "cannot accept the aforementioned treatments" was clarified, specifically by implying that even when sunitinib and everolimus where approved in China, none of them were provided by the Chinese public health insurance program. However, since this specific situation was not recorded in the CRF, it remains unknown how many patients fulfilled it. Likewise, it seems that the situation of "refusing" approved treatments was not recorded for the SANET-p trial.

Although PRRT was not approved in China at the time of conduct of both SANET trials, patients who had received it as an investigational treatment were allowed to participate. Despite of this, no patients in either trial had received PRRT upon recruitment.

The histological classification of gastroenteropancreatic NETs is in line with the latest guidelines from WHO and is endorsed. However, according to the ESMO guidelines for lung and thymic carcinoids (Baudin et al, doi.org/10.1016/j.annonc.2021.01.003), the mitotic index and presence of necrosis are validated to classify lung and thymic carcinoids as either typical or atypical, noticing that G1 is a synonym for typical carcinoid and G2 is a synonym for atypical carcinoid, which supports the G1/G2 terminology in SANET-ep.

The sought indication for surufatinib covers locally advanced and metastatic disease, regardless of line of treatment. However, regarding treatment-naïve locally advanced disease, no patients in the SANET-ep study and only two patients in the SANET-p study (both randomised to placebo) were recruited.

Considering the advanced clinical setting, the lack of baseline somatostatin receptor-based imaging constitutes an unsourmountable defect across both SANET trials. To further illustrate the imaging at baseline the Applicant should confirm: a) That all CT scans were carried out with contrast agents and in 2 or 3 phases; b) If this was the case, the Applicant should elaborate, how this was achieved in patients with allergies to contrast agents; c) For those patients who did not undergo baseline staging

with MRI of the abdomen, the Applicant should clarify, if all abdominal CTs were performed with contrast agents.

The use of two or three phasic CTs decreased slightly from baseline in both studies, when declines in renal function were more frequent. To further illustrate the imaging for response assessment the Applicant should provide more data for CT imaging with contrast agents noting the declines in renal function of the patients in both trials. This is to ensure that response assessment with two or three phasic CT in those patients for whom abdominal MRI was not used, was carried out in the given percentages, despite the declines in renal function. The Applicant should address the following questions: a) What was the guidance for CT imaging regarding renal function? Were the eCrCl rates used in it? b) For how many patients renal parameters were a contradiction for contrast enhanced CT? Were all such patients imaged with MRI during response assessment?.

The translation of the exclusion criteria in the CSR and the protocol for the SANET–ep study erroneously stated "carcinoid tumors"; this should have read "adenocarcinoid". This was stated appropriately in the original Chinese version of the protocol and has been corrected in the protocol version 4.

Treatments

Treatment regimens:

Treatment arm: Surufatinib 300 mg, QD, via oral administration, with 4 weeks as one treatment cycle

Control arm: placebo 300 mg, QD, via oral administration, with 4 weeks as one treatment cycle

Dose adjustments levels in case of toxicity:

Table 4 Dose Adjustment Reference Table

Original dose	300 mg, quaque die	Study drug, six 50 mg capsules
First dose reduction	250 mg, quaque die	Study drug, five 50 mg capsules
Second dose reduction	200 mg, quaque die	Study drug, four 50 mg capsules
Third dose adjustment*	250 mg or 200 mg, quaque die, for three consecutive weeks and discontinuation for one week, with four weeks as one treatment cycle	Study drug, five or four 50 mg capsules

Duration of treatment: Treatment was administered until disease progression, death, intolerable toxicity, withdrawal of ICF, or until termination of treatment is deemed by the study doctor to be in the patient's best interest.

Other treatments: The use of other antitumor treatments was prohibited during the study drug treatment period. However, if a patient had obvious symptoms of functional NET and required the use of long-acting somatostatin analogues (SSAs) to control the symptoms, he/she was allowed to receive short term SSA symptomatic treatment.

Cross-over: After progressive disease, unblinding was allowed and patients in the placebo arm were allowed to cross over to open-label surufatinib if they continued to meet the eligibility criteria and signed the consent to continue in the open-label phase.

4 patients from the placebo arm of SANET-ep underwent a loss of chance situation before V2 of the protocol was adopted: crossover to surufatinib was not allowed upon progression until after such amendment.

Objectives

Primary Objective:

• To assess the PFS –as determined by investigator in accordance with RECIST 1.1– of patients with advanced extrapancreatic NET treated with surufatinib as compared to those treated with placebo.

Secondary Objectives:

• To assess the ORR, disease control rate (DCR), duration of response (DoR), time to response (TTR) –as determined by investigator in accordance with RECIST 1.1– and overall survival (OS) of patients with advanced extrapancreatic NET treated with surufatinib as compared to those treated with placebo.

• To assess the safety and tolerability of surufatinib treatment in patients with advanced extrapancreatic NET.

Exploratory Objectives:

• To assess the changes in the tumor marker level in blood and urine after treatment with surufatinib as compared to the baseline.

• To assess the effect of surufatinib on the relevant biomarkers of the drug target in plasma and/or tumor tissues.

• To assess the steady state pharmacokinetic parameters of surufatinib in patients with advanced extrapancreatic NET and the correlation between surufatinib efficacy indicators and AE.

• To assess the changes in quality of life of the two groups of patients after treatment as compared to the baseline.

Outcomes/endpoints

Efficacy endpoints:

PFS is the primary efficacy variable and defined as the date of randomization to the earlier of either date of progressive disease (PD) or death by any cause. PD will be determined by designated investigator at site and BIIRC, separately.

Overall Survival (OS): OS is defined as the date of randomization to the date of death by any cause. Patients known to be alive will be censored at the last known survival follow-up date.

Best Overall Response (BOR): BOR is defined as best response achieved by individual patient until documented disease progression or the date of any subsequent anti-tumor therapy, whichever occur first.

Objective Response Rate (ORR): ORR is defined as the incidence of complete response or partial response per the RECIST v1.1.

Disease Control Rate (DCR): DCR is defined as the incidence of complete response, partial response and stable disease according to RECIST v1.1.

Duration of Response (DoR): DoR is defined as the duration between the date the criteria for CR or PR was first measured (first record shall prevail) and the date of disease recurrence or progression as objectively recorded (the reference to disease progression shall be the smallest measurable lesion recorded after treatment initiation).

Time to Response (TTR): TTR is defined as the period from the date of randomization to the date when the criteria for CR or PR was first measured (first record shall prevail).

Tumor Shrinkage: Percent changes of tumor size from baseline of target lesion will be calculated at each visit, and the best percent change per patient will be selected.

During both pivotal trials, clinical decisions for patients were dependent upon BIIRC-assessment. 11% of the patients from the studies continued receiving the same treatment even when the investigator had declared PD but the BIIRC disagreed (non-PD). The amendment that downgrades BIIRC-PFS and prioritises INV-PFS as primary endpoint while trials were ongoing is not justified.

Sample size

The calculation of sample size was based on the following assumptions:

- The total two-tailed significance level is 0.05;
- The median PFS of the control arm is 8 months;
- The hazard ratio (HR) of the trial arm to the control arm is 0.6 based on a statistical power of approximately 90%;
- The enrolment rate is approximately 10 subjects per month;
- The 24-month dropout rate is approximately 20%;
- The randomization ratio is 2:1;
- Interim analysis is conducted after obtaining 127 (70%) of the expected PFS events, and the O'Brien-Fleming boundary shape method is used to conduct α control.

Under the premise of these assumptions, the trial was expected to enrol 273 patients in approximately 28 months and the final analysis was conducted when 182 PFS events were observed.

Randomisation and blinding (masking)

This study planned to randomize (according to the ratio of 2:1) 273 patients into the following treatment arms based on the Interactive Web Response System (IWRS).

- Sulfatinib 300 mg QD, via oral administration
- Placebo 300 mg QD, via oral administration

The randomization stratification factors were: NET pathological grade (G1 or G2), prior use of systemic anti-tumor drug therapy (yes or no), primary tumor lesion site: A (jejunum, ileum, duodenum, thymus, cecum) or B (lung, stomach, liver, appendix, colon, rectum) or C (other origins or unknown origins).

The clinical paradigm to justify stratification of extrapancreatic NETs in three categories (A-B-C) according to primary tumour sites is not valid: the prognostic data used as a reference to establish such categorisation (Yao et al, J Clin Oncol 2008) do not correspond to the categories that were established for SANET-ep.

Subjects were randomized to the surufatinib treatment arm or the corresponding placebo treatment arm in accordance with the double-blind method. Study personnel participating in the trial [including investigators, sponsor personnel, contract research organization personnel, site pathology reviewers, independent central imaging evaluators, sample analysts and statisticians, but except independent data monitoring committee (IDMC) members] and subjects did not know what drug treatment to which they are assigned. The investigator obtained the randomization number assigned to the subjects based on the information provided by the IWRS.

An unblinded third-party statistician independent from the study project team communicated with the IDMC members on the interim analysis results. Based on the unblinded interim analysis results, the IDMC members announced the decision whether to continue with the study to this study project team without disclosing any interim analysis results and data.

In the double-blind study phase, apart from emergency unblinding, the investigator could only unblind a subject if the BIIRC determined that the subject had PD and the investigator decided to terminate the subject's blinded treatment. Before unblinding, the subject completed the end-of-double-blind-treatment visit, and the investigator completed all evaluations of the subject's blinded clinical data and recorded it in the electronic case report form (eCRF).

The randomization list was created by a CRO based on protocol requirement. A block size of 3 was selected to reduce imbalance in the strata given the limited sample size.

Statistical methods

Analysis sets:

Full subject set / All subject set: This included all subjects who signed the ICF. This analysis set was mainly used for the subject distribution summary table and all lists.

Intention-to-treat analysis set (ITT set): This included all randomized subjects. According to the principles of the intention-to-treat analysis, subjects were analyzed based on the treatment arm they were randomized to and stratification factors. The ITT set was the primary analysis set for the efficacy endpoints of PFS and OS of this interim analysis.

Interim intention-to-treat analysis set (iITT set): This analysis set was mainly used for the analysis of best overall response (BOR), ORR, DCR, DoR and TTR in the interim analysis. This included subjects who met at least one of the following criteria in the ITT set:

Received at least one post-baseline tumor evaluation $\geq$ 6 weeks after the first drug administration

Discontinued the double-blind study treatment for any reason.

Per protocol analysis set (PP set): This included subjects in the ITT set with no major protocol deviations that could affect the efficacy evaluation. The PP set was used for the sensitivity analysis of the primary efficacy endpoints.

Primary endpoint PFS:

The primary analysis of PFS will be based on investigator assessment. It will be performed using ITT set and will use the default censoring and event date option from Table 2 (p. 31/94 SAP), Section 7.2.1 i.e. A, B, C1(1), C2(1), D, E and F.

The difference in PFS between sulfatinib and placebo will be tested using the stratified log-rank test with two-side alpha level of 0.015 at interim analysis or 0.045 at final analysis (Note the exact significance level will be determined based on the actual number of PFS events at interim analysis.). The strata used for the test include the stratification factors from IWRS. This will be the primary test for PFS.

It is likely that stratum cell sizes might be too small, especially at interim analysis. In that case, to allow stratified analysis to work well, correlated small stratum cells may be combined to form new stratum cell(s). Alternatively, drop one or more stratification factor(s) from the stratification analysis. The strategy of collapsing stratum cells will be determined at the Blinded Data Review Meeting. The decision will be documented in Blinded Data Review Report.

For each treatment group, the Kaplan-Meier estimate of PFS survival function will be constructed. Hazard ratio of sulfatinib vs. placebo of PFS with two-sided 95% CI will be derived from the stratified Cox proportional hazard model.

Table 10. Censoring Scheme for PFS/DoR

	Situation	Date of Progression or Censoring	Outcome
A	No baseline assessment or no post-baseline tumor assessment	Date of randomization[a]	Censored
B	Progression or death at or before next scheduled tumor assessment	Date of progression (or death)	Progressed
C1	Progression or death after exactly one missing/non-evaluable tumor assessment[c]	1) Date of progression (or death) 2) Date of next scheduled assessment[b]	Progressed Progressed
C2	Progression or death after two or more consecutive missing/non-evaluable tumor assessments [c]	1) Date of last adequate assessment before the date of progression (or death) 2) Date of next scheduled assessment[b]	Censored Progressed
D	No progression and no death	Date of last adequate assessment	Censored
E	Treatment discontinuation for undocumented progression, i.e. clinical progression based on investigator claim	NA	Ignored. Outcome derived based on RECISIT evaluation only
F	Additional anticancer therapy (including open-label Sulfatinib) started prior to documented disease progression or death on study	Date of last adequate assessment on or before start of new anticancer therapy.	Censored

[a] The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death
[b] Refers to the next scheduled tumor assessment after the date of the last tumor assessment
[c] Time period that identifies two consecutive missed/non-evaluable tumor assessments is calculated 2*(the protocolled time between scans + the protocol allowed visit window) of randomization or the

Source SAP for Study 2015-012-00CH4 page 31/94.

Sensitivity analyses for PFS:

Sensitivity Analysis 1: Using the investigator assessments on the PPS and using the same conventions as for the primary analysis.

Sensitivity Analysis 2: Using the BIRC assessments on the ITT set and using the same conventions as for the primary analysis

Sensitivity Analysis 3: Using the investigator assessments on the ITT set and using the same conventions as for the primary analysis, with the exception of using a different censoring and event date option from Table 2, i.e. A, B, C1(2), C2(2), D, E and F, i.e. backdating of events occurring after missing tumor assessments. In the summary tables, this approach is referred as "backdating PFS analysis.

Sensitivity Analysis 4: Using the investigator assessments on the ITT set and using the same conventions as for the primary analysis, with the exception of using the stratification factors collected by eCRFs and from central pathology review for stratified log-rank test and stratified Cox proportional hazard model

Sensitivity Analysis 5: An unstratified logrank test will be performed for investigator data in ITT set. HR and its 95% CI will be estimated from unstratified Cox proportional hazard model.

Secondary endpoints: Objective response rate (ORR) and disease control rate (DCR):

The exact 95% confidence interval for ORR or DCR will be calculated for each treatment group respectively using the Clopper-Pearson method. The treatment difference will be tested using Cochran-Mantel-Haenszel (CMH) exact test, with baseline stratification factors as strata. The results from the CMH exact test will be expressed in terms of the common odds ratio and its exact 95% confidence interval and p-value. Note that it is anticipated that the ORR in this study might be very low, which makes unstratified analysis is more appropriate. In that case, the treatment difference in ORR will be tested using Fisher's exact test and the 95% confidence interval for ORR will be calculated using exact method. Note that small strata may be combined together to form larger strata for CMH analysis.

Patients with BOR of 'NE' will be considered non-responders and will be included in the denominator when calculating the response rate.

The primary analysis of ORR and DCR will be based on investigator assessment. Supportive analysis of ORR and DCR will be performed based on BIIRC assessment. Another supportive analysis will be performed using the confirmed ORR and DCR by investigator and BIIRC separately.

In SANET-ep, the final stratum in the primary analysis of PFS and all the other stratified analyses was: NET pathological grade (G1 or G2), prior use of systemic anti-tumor drug therapy (yes or no), primary tumor lesion site: A/C (jejunum, ileum, duodenum, thymus, cecum, other origins or unknown origins) (subjects reported to have primary lesions in the "small intestine" was also be classified as A) or B (lung, stomach, liver, appendix, colon, rectum).

In SANET-p, the final stratum was NET pathological grade G1 regardless previous systemic anti-tumor drug for advanced disease and ECOG PS value, NET pathological grade G2 by previous systemic anti-tumor drug for advanced disease (yes, no) and ECOG PS (0, 1).

The alpha level was based on a spending function from the O'Brien-Fleming formula.

The censoring rules for PFS are not endorsed since start of a new anticancer therapy or lack of compliance with study visit can be due to PD. The results of several sensitivity analyses were summarised, but PFS still was not tested using the censoring rules from Table 2 in SAP v. 3:

Situation	Assigned to surufatinib	Assigned to placebo
A	Censored	Censored
B	Event	Event
C1	Event	Event
C2	Event one day after the last adequate assessment	Censored one day after the last adequate assessment
D	Censored	Censored
E	Not applicable	Not applicable
F	Event	Censored

The analyses should be performed using the ITT and the i-ITT for both pivotal studies, and the BICR and investigator's assessments. The analyses should be also performed with all the stratification factors if possible and/or with only those that the Applicant consider feasible, and unstratified.

Multiplicity adjustment and interim analysis:

An interim analysis, that allows for stopping the study for superior efficacy is planned when approximately 127 (70%) of the PFS events have been documented in the ITT population. An alpha-spending function due to Lan DeMets (1983) with O'Brien-Fleming type stopping boundary will be used

for the interim efficacy analysis. Therefore, if the interim analysis is performed exactly after 127 events have been documented, a nominal p-value of less than 0.015 (corresponding to an upper bound of hazard ratio = 0.631) will need to be observed to declare statistical significance.

The critical values of nominal p-value and hazard ratio that will be used to declare statistical significance at the interim analysis will be calculated based on the actual number of PFS events documented at the time the interim analysis. The interim analyses will be performed by an independent statistician external to the study team. The results of the interim analyses will be presented to the IDMC by the independent statistician. The IDMC will provide the Sponsor with a recommendation to continue the trial as planned, to have an interruption, to make a protocol amendment, or to terminate the trial. If the interim analysis demonstrates significant prolongation of PFS in sulfatinib group compared to control group, IDMC could recommend to terminate and unblind the study, and the study could be announced as completed. The study data from open-label phase are not in the scope of the planned interim analysis. Once it is decided to stop the trial based on the interim analysis results, the open-label data will be analysed together with the remainder data analysis for double blind phase.

Changes to the planned analyses:

The following analyses are not described in the study protocol but added to this analysis plan:

Additional analysis populations are defined as follows:

Open-label set

i-ITT set

All subjects set

Exploratory analysis into the potential influence of baseline covariates on the primary efficacy variable PFS.

'Tumor Shrinkage' is added to the secondary efficacy endpoint and analysis methods are described

Changes to statistical methods:

95% confidence interval of treatment difference in DCR and ORR will be derived using exact method rather than normal approximation.

EORTC QLQ-C30 and QLQ-GI.NET21 data will only be analyzed using descriptive summary statistics given its nature of exploratory analysis.

Results

Participant flow

Figure 16. Participant flow from SANET-ep, all subjects

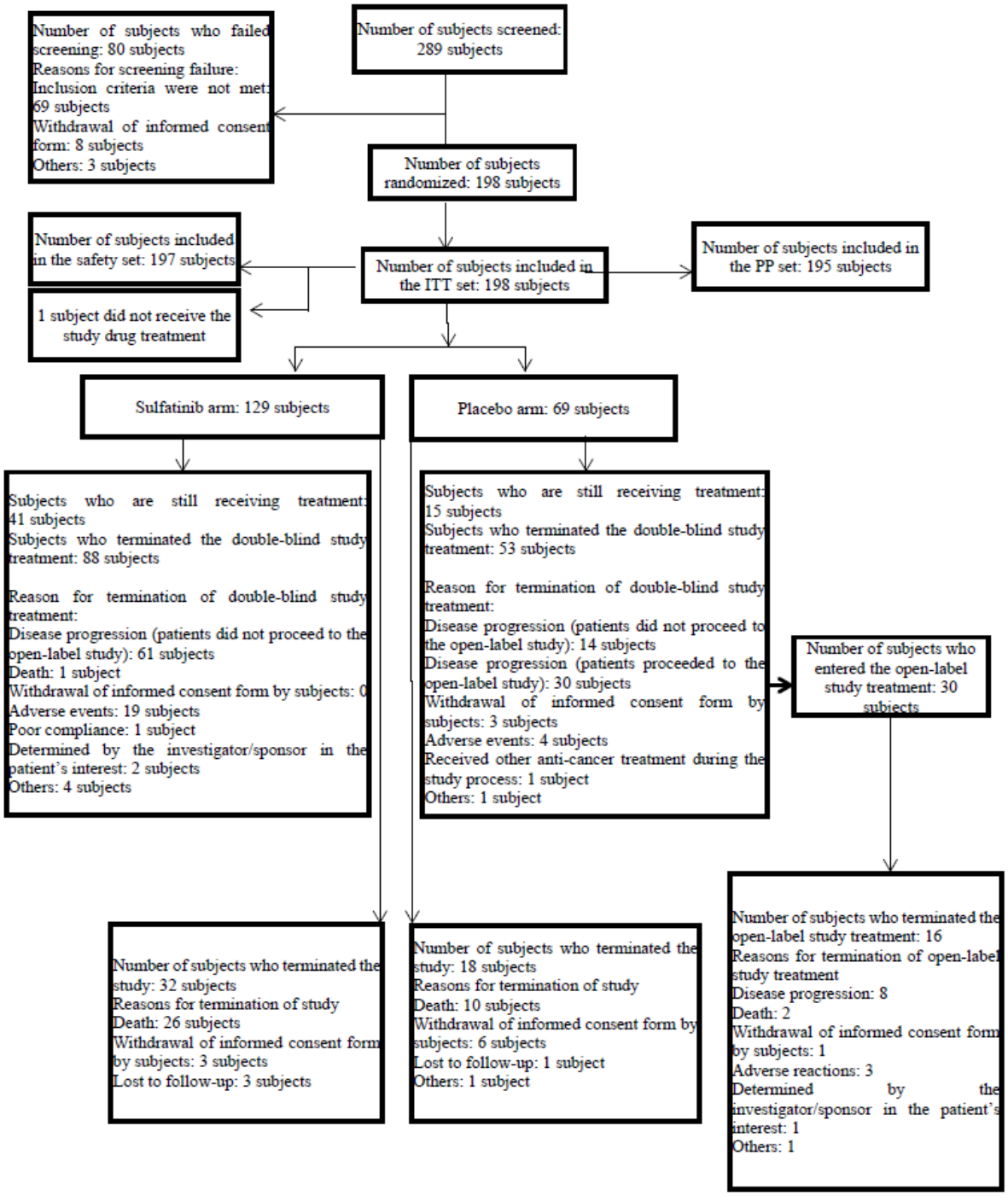


Table 11. Patient disposition from SANET-ep, all subjects

Description	Sulfatinib Arm n (%)	Placebo Arm n (%)	Total n (%)
Number of subjects screened			289
Screening failure			80
Reasons for screening failure			
All inclusion criteria were not met			69
Withdrawal of informed consent form			8
Others			3
Number of subjects randomized (a)	129	69	198 (68.5)
Number of subjects who received treatment (b)	129 (100.0)	68 (98.6)	197 (99.5)
Number of subjects who are still receiving the double-blind study treatment (c)	41 (31.8)	15 (22.1)	56 (28.4)
Number of subjects who terminated the double-blind study treatment (c)	88 (68.2)	53 (77.9)	141 (71.6)
Reason for termination of double-blind study treatment:			
Disease progression (patients did not proceed to the open-label study)	61 (47.3)	14 (20.6)	75 (38.1)
Disease progression (patients proceeded to the open-label study)	0	30 (44.1)	30 (15.2)
Death	1 (0.8)	0	1 (0.5)
Withdrawal of informed consent form by subjects	0	3 (4.4)	3 (1.5)
Adverse event	19 (14.7)	4 (5.9)	23 (11.7)
Poor compliance	1 (0.8)	0	1 (0.5)
Received other anti-tumor treatment during the study process	0	1 (1.5)	1 (0.5)
Determined by the investigator/sponsor in the patient's interest	2 (1.6)	0	2 (1.0)
Others	4 (3.1)	1 (1.5)	5 (2.5)
Number of subjects who terminated the open-label study treatment (d)		16 (53.3)	16 (53.3)
Reasons for termination of open-label study treatment			
Disease progression		8 (26.7)	8 (26.7)
Death		2 (6.7)	2 (6.7)
Withdrawal of informed consent form by subjects		1 (3.3)	1 (3.3)
Adverse event		3 (10.0)	3 (10.0)

Protocol deviations:

Table 14.1.1.3 Summary of Major Protocol Deviations during Double Blind Treatment Phase - ITT Set

Site: Overall

	Sulfatinib (N = 129) n (%)	Placebo (N = 69) n (%)	Total (N = 198) n (%)
At least one major protocol deviation	7 (5.4)	5 (7.2)	12 (6.1)
Inclusion / Exclusion	1 (0.8)	1 (1.4)	2 (1.0)
Informed Consent Deviations	1 (0.8)	2 (2.9)	3 (1.5)
Other	3 (2.3)	1 (1.4)	4 (2.0)
Prohibit Medication	0	2 (2.9)	2 (1.0)
Study Drug	2 (1.6)	1 (1.4)	3 (1.5)

This table include all major protocol deviations that are identied and determined at Blinded Data Review Meeting.
Not all major protocol deviations will lead to exclusion of subjects from per-protocol set unless they may affect efficacy evaluation.

69% (61 out of 88) of patients from the surufatinib arm and 83% (44 out of 43) from the placebo arm terminated double blind phase because of PD. From the 44 progressors in the placebo arm, 30 were crossed over to surufatinib.

3 patients from the placebo arm were declared as progressors by the investigator but were not crossed over to surufatinib because BIIRC disagreed (non-PD) and clinical decisions for the patients were dependent on BIIRC. 11 patients from the placebo arm were declared as progressors by both investigator and BIIRC but were not crossed-over to surufatinib becase they did not sign the informed consent to enter the open-label part of the study.

Recruitment

First patient randomised:	17-DEC-2015
Primary PFS analysis (data cut-off date):	31-MAR-2019
iDMC disclosure of interim analysis results:	12-JUN-2019
Last patient randomised:	28-JUN-2019
Study unblinding (termination of study):	04-JUL-2019
OS update (data cut-off date):	20-OCT-2020

At interim analysis of PFS, performed on 31-MAR-2019, the median duration of follow-up (time from date of randomization to date of PD/death or censoring using reverse Kaplan-Meier methodology) was 13.8 months (95% CI: 11.1, 16.7) in the surufatinib arm and 16.6 months (95% CI: 9.2, not evaluable [NE]) in the placebo arm.

At updated OS analysis, performed on 30-OCT-2020, the median follow-up time was 31.5 months (95% CI: 26.6, 34.1) in the surufatinib arm and 31.1 months (95% CI: 25.3, 38.1) in the placebo arm.

For SANET-ep 28 sites were involved, of which 24 managed to enroll patients. Highest number of enrolled patients (55) came from The Fifth Medical Center of Chinese PLA General Hospital (formerly Beijing 307 Hospital, Academy of Military Medical Sciences), 8 Dongdajie Street, Fengtai District, Beijing.

For SANET-p 27 sites were involved, of which 25 managed to enroll patients. Again, the highest number of enrolled patients (39) came from The Fifth Medical Center of Chinese PLA General Hospital (formerly Beijing 307 Hospital, Academy of Military Medical Sciences), Beijing.

The applicant is requested to confirm that the patient randomised to the placebo arm after the interim analysis notice did factually receive placebo treatment and present a brief clinical narrative to date. The applicant is further requested to justify why any patients were recruited after interim analysis notice, if according to protocol this implied early termination of the study.

Conduct of the study

The original protocol (08-SEP-2015) was amended twice during the study. Protocol Amendment 1 (Version 2.0) was released on 02-NOV-2016, and Protocol Amendment 2 (Version 3.0) was released on 19-OCT-2017.

<u>Main changes implemented in Protocol Amendment 1 (02-NOV-2016, Version 2.0)</u>

- Inclusion Criteria: The provisions on the past anti-tumor drug treatment regimens of the target population was revised.
- Termination of study treatment or termination of study by patients: The requirements for termination of treatment by patients in the double-blind treatment phase were revised, i.e. the patients in the

double-blind treatment phase should continue to receive treatment until he/she experiences disease progression based on imaging evaluation conducted by the site.

- Unblinding after disease progression determined by BIIRC: Additional requirements and procedures were added for unblinding after disease progression determined by BIIRC.
- Safety evaluation: Additional visits were added to strengthen the monitoring of common adverse reactions.
- End-of-double-blind-treatment visit: Additional requirements and procedures for the end-of-double-blind treatment visit were added for patients who are about to be unblinded.
- Open-label study phase: Additional requirements and procedures were added for the open-label study phase.
- Survival follow-up period: The part on "patients who did not experience disease progression after the end of the double-blind study treatment should continue to undergo tumor evaluation based on the protocol until he/she experiences disease progression determined by BIIRC" was revised.
- Study drug randomization/drug supply protocol: The portion on drug supply arrangements of the open-label study phase was supplemented.
- Drug storage: The maximum temperature for drug storage was revised.
- Drug administration method: It is recommended to take the drug at the same time point every day, and the description of the exact time of drug collection and administration on the first day of drug administration was added.
- Precautions: Observation data and management recommendations for hypertension were added. The anti-hypertensive drug, calcium channel blockers is mainly metabolized by CYP3A4 and Sulfatinib has time-dependent inhibitory effect on CYP3A4/5 based on the study data. Hence, patients' blood pressure should be closely monitored when Sulfatinib is used in combination with calcium channel blockers.
- The dose adjustment strategy and adverse reaction management of Sulfatinib were revised in accordance with the management experience of adverse reactions in the phase Ib/II study 65 of Sulfatinib in patients with NET.
- Drug interactions: According to the new study data, a description was added to show the time-dependent inhibitory effect of Sulfatinib on CYP3A4/5.
- Study flowchart: Additional visits were added to Table 5 Flowchart of Double-Blind Study Phase, so as to strengthen the monitoring frequency of adverse reactions.
- Study flowchart: Table 6 Study Flowchart of Open-label Treatment Phase was added to clarify the operating requirements for study procedures of the open-label treatment phase.
- 30-day end-of-treatment visit: The visit name was revised to distinguish from the end-of-double-blind-treatment visit.
- Safety evaluation indicators: An explanation was provided to state that cardiac monitoring is required during the end-of-double-blind-treatment visit.
- Interim analysis: The interim analysis plan was adjusted to increase the statistical power of the interim analysis, and a description on the fixed statistical calculation process of the interim analysis plan was provided.

- Appendix 3. Guiding Principles on Potential Interaction Between Sulfatinib and Concomitant Medications: According to the new study data, a description was added to show the time-dependent inhibitory effect of Sulfatinib on CYP3A4/5.
- Appendix 3 - Table 3 Substrates of CYP3A Enzyme: This form was added to list the substrates of CYP3A enzyme.

Main changes implemented in Protocol Amendment 2 (19-OCT-2017, Version 3.0)

- Clinical protocol summary, Table 5 Double-Blind Phase Study Flowchart Comment 15, safety evaluation, evaluation of pharmacokinetic indicators, pharmacokinetic (PK) test and Table 7 Pharmacokinetic Sample Collection Schedule: The time window for C1D15 in the protocol flowchart was +/-1 day, but this time window was not stated in the other sections of Protocol Version 2.0. Hence, the part on "the time window for C1D15 visit is +/-1 day" was clarified in the corresponding part of Protocol Version 3.0 to ensure consistency with the content of the text.
- Clinical protocol synopsis, overall study design, trial completion and end-of-study unblinding: A description was added to state that patients who are still receiving Sulfatinib treatment after unblinding of the entire study shall roll over to another open-label study and receive the Sulfatinib treatment.
- Clinical protocol synopsis, primary efficacy endpoint analysis: The statistical analysis of the primary study endpoint was mainly revised based on the tumor evaluation data determined by the investigator, and the tumor evaluation data of the BIIRC was used as the supporting analysis.
- Study flowchart, tumor markers and biomarkers, testing of biomarkers: In Protocol Version 2.0, the biomarker blood samples were collected after disease progression. However, it was clarified in Protocol Version 3.0 that blood samples for the biomarker study were collected after investigators evaluated the tumor to be disease progression.
- Table 5 Double-blind Phase Study Flowchart Comment 23 and 30-day end-of-treatment visit: It was mentioned in Protocol Version 2.0 that if a patient has ended the double-blind study treatment but was not determined by BIIRC to have disease progression, he/she was recommended to continue to undergo tumor evaluation during this visit and should return to the study site regularly for tumor evaluation until the patient has disease progression determined by the BIIRC, was lost to follow-up or died. In Protocol Version 3.0, a supplementary explanation was provided that if a subject has reached disease progression determined by the investigator and BIIRC, the subject can choose not to undergo tumor imaging evaluation in the visit.

Main changes implemented in Protocol Amendment 3 (07-AUG-2019, Version 4.0)

Based on the interim analysis results (data cut-off date [DCO] March 31, 2019), the IDMC expert group of this study determined that the primary endpoint PFS of this study had reached the predetermined significance level specified in the protocol, and the study could be terminated early. The company accepted the IDMC expert group recommendation to terminate the blinded study and unblind all subjects. At the end of the blinded study, subjects who are still in this study can all proceed to the roll-over open-label study phase. The purpose of this protocol amendment is to provide guidance for the subsequent treatment, follow-up arrangements and data collection of such subjects.

All study sites will be unblinded after the end of the blinded study phase. At the end of the blinded study, subjects who are still in this study may enter the roll-over open-label study phase, and the patient visits shall be scheduled according to the open-label study phase. Refer to Table 6 Open-label Phase Study Flowchart and remarks for details.

For patients who are still receiving blinded treatment and are in the placebo arm after unblinding, after the patients re-sign the informed consent form of the open-label study phase, complete the screening of the open-label study phase and are found to meet the screening criteria (refer to the open-label study phase for details), they can receive surufatinib treatment until the investigator determines that there is progressive disease, intolerable toxicity or other criteria for termination of treatment specified in the protocol are met.

Patients who are still receiving blinded treatment and are in the surufatinib arm after unblinding can continue to receive surufatinib treatment until the investigator determines that there is progressive disease, intolerable toxicity or other criteria for termination of treatment specified in the protocol are met. The visit schedule of patients shall be carried out according to the open-label study phase. Refer to Table 6 Open-label Phase Study Flowchart and remarks for details.

Patients who have been receiving open-label treatment with surufatinib before the end of the blinded study will continue to undergo visits and follow-ups in accordance with the requirements of the open-label study phase, until the investigator determines that there is progressive disease, intolerable toxicity or other criteria for termination of treatment specified in the protocol are met.

Patients who have terminated the study treatment prior to the end of the blinded study and have entered the survival follow-up period will continue to undergo survival follow-up in accordance with the protocol. During the roll-over open-label study phase, the sponsor will no longer provide tumor evaluation fees, and the investigator can arrange for tumor evaluation on his own based on routine clinical practice; the sponsor will provide safety assessment and collect the relevant safety assessment data, study drug medication information, and survival follow-up data (including subsequent anti-tumor treatment). The roll-over open-label study phase will continue until surufatinib is marketed or the sponsor terminates the entire study based on the research and development status of this drug.

Baseline data

Table 12. Patient demographics and baseline characteristics – ITT set study SANET-ep

Demographic characteristics	Sulfatinib Arm N=129	Placebo Arm N=69	Total N=198
Age (years)			
n	129	69	198
Mean (standard deviation)	50.98 (11.855)	52.83 (11.837)	51.63 (11.851)
Median	52.00	54.00	52.50
Minimum, maximum	19.0, 72.0	25.0, 79.0	19.0, 79.0
Age group, n (%)			
< 65 years old	115 (89.1)	56 (81.2)	171 (86.4)
≥ 65 years old	14 (10.9)	13 (18.8)	27 (13.6)
Gender, n (%)			
Male	73 (56.6)	35 (50.7)	108 (54.5)
Female	56 (43.4)	34 (49.3)	90 (45.5)
Race, n (%)			
Asian	129 (100.0)	69 (100.0)	198 (100.0)
Chinese	129 (100.0)	69 (100.0)	198 (100.0)
Smoking status, n%			
Never	78 (60.5)	47 (68.1)	125 (63.1)
Yes	13 (10.1)	8 (11.6)	21 (10.6)
Quit smoking	38 (29.5)	14 (20.3)	52 (26.3)
ECOG PS，n (%)			
0	72 (55.8)	46 (66.7)	11 (59.6)
1	57 (44.2)	23 (33.3)	80 (40.4)
Height (cm)			
n	129	69	198
Mean (standard deviation)	165.64 (8.425)	165.05 (8.206)	165.43 (8.333)
Median	166.00	165.00	165.00
Minimum, maximum	140.0, 185.0	150.0, 183.0	140.0, 185.0
Body weight (kg)			
n	129	69	198
Mean (standard deviation)	63.85 (12.339)	63.38 (10.429)	63.69 (11.684)
Median	63.00	62.50	63.00
Minimum, maximum	37.0, 100.0	42.0, 100.5	37.0, 100.5
BMI（kg/m^2）			
n	129	69	198
Mean (standard deviation)	23.18 (3.675)	23.25 (3.348)	23.20 (3.556)
Median	23.20	23.20	23.20
Minimum, maximum	16.0, 36.7	17.1, 34.8	16.0, 36.7

Table 13. Baseline tumour characteristics – ITT set study SANET-ep

Baseline Tumor Characteristics	Sulfatinib Arm N=129	Placebo Arm N=69	Total N=198
Time interval between the first diagnosis and time of randomization (months)			
n	129	69	198
Mean (standard deviation)	28.65 (39.162)	24.48 (27.310)	27.19 (35.467)
Median	15.70	14.55	15.59
Minimum, maximum	0.8, 303.2	1.2, 145.5	0.8, 303.2
Primary tumor site, n (%)			
Gastrointestinal tract	61 (47.3)	32 (46.4)	93 (47.0)
Stomach	10 (7.8)	9 (13.0)	19 (9.6)
Small intestine	10 (7.8)	6 (8.7)	16 (8.1)
Colon	2 (1.6)	2 (2.9)	4 (2.0)
Appendix	1 (0.8)	0	1 (0.5)
Rectum	38 (29.5)	15 (21.7)	53 (26.8)
Others	68 (52.7)	37 (53.6)	105 (53.0)
Unknown	18 (14.0)	9 (13.0)	27 (13.6)
Lung	12 (9.3)	11 (15.9)	23 (11.6)
Thymus	10 (7.8)	4 (5.8)	14 (7.1)
Liver	9 (7.0)	2 (2.9)	11 (5.6)
Mediastinum	8 (6.2)	3 (4.3)	11 (5.6)
Corresponding stratification of the primary tumor site recorded in the CRF, n (%)			
A (jejunum, ileum, duodenum, thymus, cecum)	20 (15.5)	10 (14.5)	30 (15.2)
B (lung, stomach, liver, appendix, colon, rectum)	72 (55.8)	39 (56.5)	111 (56.1)
C (includes other origins or unknown origins)	37 (28.7)	20 (29.0)	57 (28.8)
Site pathological grade n (%)			
G1	21 (16.3)	11 (15.9)	32 (16.2)
G2	108 (83.7)	58 (84.1)	166 (83.8)
Stage of disease, n (%)			
IV	129 (100.0)	69 (100.0)	198 (100.0)
Metastatic site, n (%)			
Liver	97 (75.2)	53 (76.8)	150 (75.8)
Lymph nodes	61 (47.3)	33 (47.8)	94 (47.5)
Lung	33 (25.6)	18 (26.1)	51 (25.8)
Bone	40 (31.0)	26 (37.7)	66 (33.3)
Brain	1 (0.8)	0	1 (0.5)
Others	48 (37.2)	26 (37.7)	74 (37.4)
Number of tumor-affected organs, n (%)			
<= 2	43 (33.3)	25 (36.2)	68 (34.3)

>= 3	86 (66.7)	44 (63.8)	130 (65.7)
NET functional status, n (%)			
Functional	5 (3.9)	2 (2.9)	7 (3.5)
Non-functional	122 (94.6)	67 (97.1)	189 (95.5)
Unknown	2 (1.6)	0	2 (1.0)
Time interval between last disease progression before enrollment and randomization (months)			
n	129	69	198
Mean (standard deviation)	1.47 (1.426)	1.70 (1.573)	1.55 (1.479)
Median	0.99	1.22	1.05
Minimum, maximum	0.1, 9.7	0.1, 8.5	0.1, 9.7
≤ 3 months	114 (88.4)	58 (84.1)	172 (86.9)
> 3 months	15 (11.6)	11 (15.9)	26 (13.1)
Received prior systemic anti-tumor drug therapy for advanced tumors, n (%)			
Yes	89 (69.0)	44 (63.8)	133 (67.2)
No	40 (31.0)	25 (36.2)	65 (32.8)
Received prior everolimus therapy, n (%)			
Yes	10 (7.8)	8 (11.6)	18 (9.1)
No	119 (92.2)	61 (88.4)	180 (90.9)
Received prior somatostatin therapy, n (%)			
Yes	44 (34.1)	19 (27.5)	63 (31.8)
No	85 (65.9)	50 (72.5)	135 (68.2)
Prior systemic chemotherapy, n (%)			
Yes	52 (40.3)	27 (39.1)	79 (39.9)
No	77(59.7)	42 (60.9)	119 (60.1)
Received prior antiangiogenic drug therapy, n (%)			
Yes	1 (0.8)	1 (1.4)	2 (1.0)
No	128 (99.2)	68 (98.6)	196 (99.0)

Source: Statistical Table 14.1.2.1

Abbreviations: CRF = case report form, NET = neuroendocrine tumor.

Note: N = number of patients of each treatment arm in the analysis set. n = number of patients in a specific category.

The internal distribution of G1 (16%) and G2 (84%) in SANET-ep does not seem to reflect the much higher incidence of G1 tumours in clinical practice, (e.g. Korse et al; https://doi.org/10.1016/j.ejca.2012.12.022). Although this can be considered a product of coincidence, this situation adds up in lack of external validity of the results of the pivotal trials.

Eleven patients had primary tumour location as mediastinum, which are extremely rare ocurrences. It was not further clarified by the applicant whether this clinical scenario was confirmed, noting that somatostatin receptor-based imaging at baseline –essential for diagnosis and staging, as by Chinese treatment guidelines 2013 and 2016– was not utilised in either pivotal trial.

The Applicant should provide subgroup analyses for PFS separately for patients with one line of prior systemic therapy and with two lines of prior therapies for both trials.

Liver metastases can be treated with liver-directed interventions (e.g. SIRT). The Applicant should provide a summary of the patients, who underwent liver-directed therapies before enrollment summarizing only those interventions, which were directed to the metastatic disease (e.g. resection of liver metastases, SIRT, RFA, TACE). The Applicant should further clarify, how many had these procedures and which procedures were used. The Applicant should also provide details, whether patients with phaechromocytoma or paraganglioma were included in the study (as indicated in the listings table provided) and if yes, how many such patients were enrolled and why they were enrolled.

In EU liver-directed therapies on top of surgery are offered to patients with NETs. The Applicant should provide the frequencies for liver-directed therapies (chemoembolization, radiofrequency ablation, microwave treatment, Argon-Helium Knife ablation and alcohol injection) for both SANET-EP and SANET-P trials. This is needed in order to evaluate similarities and differences in the trial populations versus patients treated in the EU context.

Numbers analysed

Table 14. Analysis datasets – SANET-ep

	Surufatinib n (%)	Placebo n (%)	Total n (%)
All patient set			289
Randomized and enrolled	129	69	198
Intent-to-treat analysis set (ITT)[a,b]	129 (100.0)	69 (100.0)	198 (100.0)
Per protocol analysis set (PP)[c,d]	129 (100.0)	66 (95.7)	195 (98.5)
Interim intent-to-treat analysis set (iITT)[d,e]	126 (97.7)	64 (92.8)	190 (96.0)

CSR=clinical study report; ITT=intent-to-treat; iITT=interim intent-to-treat; PP=per protocol.

[a] The percentages were based on the number of patients randomized.

[b] The ITT set included all randomized and enrolled patients.

[c] The PP set included all patients from the ITT set with no major protocol deviations that have an effect on the efficacy evaluation.

[d] The percentages were based on the ITT set.

[e] The iITT set included patients in the ITT set who met at least 1 of the following criteria: (1) had at least 1 post-baseline evaluable tumor assessment after the randomized treatment (at least 6 weeks) (2) terminated the double-blind study treatment for any reason.

Source: Table 14.1.1.2 from the Study 2015 012-00CH4 CSR

Outcomes and estimation

Table 15. Primary endpoint – INV-assessed PFS in ITT at interim analysis 31-MAR-2019:

	Investigator-Assessed (Primary Endpoint)		BIIRC-Assessed (Supportive Analysis)	
	Surufatinib (N=129)	Placebo (N=69)	Surufatinib (N=129)	Placebo (N=69)
Number of PFS events, n (%)	**77 (59.7)**	**51 (73.9)**	**80 (62.0)**	**41 (59.4)**
Death, no RECIST-defined PD[a]	3 (3.9)	1 (2.0)	1 (1.3)	0
RECIST-defined PD[a]	74 (96.1)	50 (98.0)	79 (98.8)	41 (100.0)
Number censored, n (%)	52 (40.3)	18 (26.1)	49 (38.0)	28 (40.6)
PFS (months), median (95% CI)[b]	**9.2 (7.4, 11.1)**	**3.8 (3.7, 5.7)**	**7.4 (5.6, 9.3)**	**3.9 (3.7, 5.8)**
Stratified HR (95% CI)[c]	0.334 (0.223, 0.499)		0.657 (0.442, 0.977)	
Stratified log-rank p-value (2-sided)[d]	<0.0001		0.0372	
PFS rate (95% CI)[e]				
6 months	67.8 (58.0, 75.8)	33.5 (21.2, 46.2)	58.1 (48.3, 66.6)	35.6 (22.6, 48.8)
12 months	36.4 (26.5, 46.3)	14.4 (6.3, 25.7)	30.4 (21.4, 40.0)	19.9 (9.5, 33.1)
18 months	19.1 (10.6, 29.4)	4.8 (0.9, 14.0)	16.2 (8.2, 26.6)	15.0 (5.3, 29.3)
24 months	11.9 (4.9, 22.2)	0.0 (0.0, 0.0)	9.7 (3.1, 20.8)	15.0 (5.3, 29.3)

BIIRC=Blinded Independent Image Review Committee; CI=confidence interval; CSR=clinical study report; HR=hazard ratio; ITT= intent-to-treat; IWRS=interactive web response system; NET=neuroendocrine tumor; PD=progressive disease; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors.

Note: PFS refers to the time interval from the date of randomization to the first recorded PD or death due to any reason.

[a] Percentages were calculated based on the number of events.

[b] The Kaplan-Meier method was used. The 2-sided 95% CI was calculated based on the Brookmeyer and Crowley method.

[c] Based on the stratified Cox proportional hazard progression model. The stratification factors were NET pathological grade (G1, G2), previous systemic antitumor drug for advanced disease (yes, no), and primary lesion of tumor in A+C (jejunum, ileum, duodenum, thymus gland, caecum, and other origin or unknown origin) or B (lung, stomach, liver, appendix, colon, and rectum). All factors were per IWRS.

[d] From the 2-sided stratified log-rank test. The stratification factors were NET pathological grade (G1, G2), previous systemic antitumor (yes, no), and primary lesion of tumor in A/C (jejunum, ileum, duodenum, thymus, caecum, and other origin or unknown origin) or B (lung, stomach, liver, appendix, colon, and rectum). All factors were per IWRS.

[e] Calculated using the Kaplan-Meier method and Greenwood formula for variance and log-log transformation.

Source: Table 14.2.1.1 and Table 14.2.1.3 from the Study 2015-012-00CH4 CSR

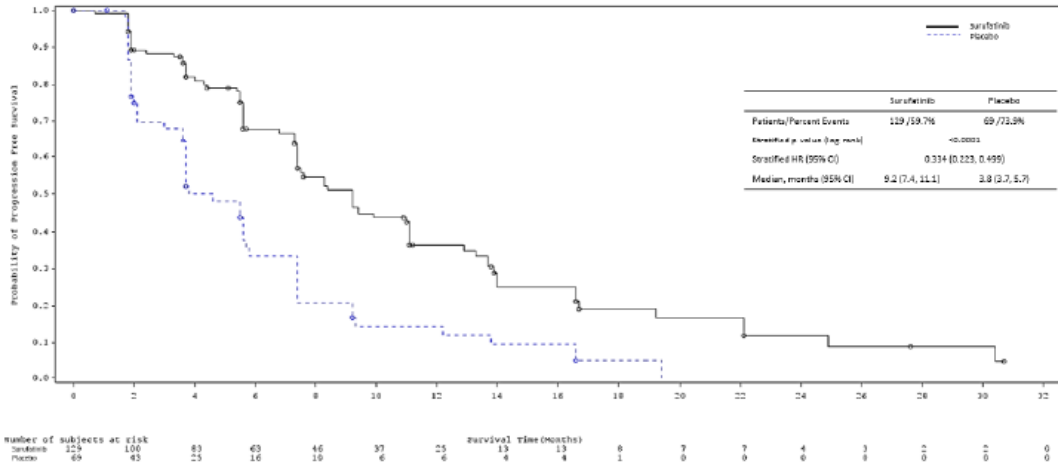
Table 9 PFS Analysis (Investigators' Evaluation) - ITT Set

	Sulfatinib Arm (N = 129)	Placebo Arm (N = 69)
Subjects involved in PFS events	77 (59.7)	51 (73.9)
Death, no RECIST-defined disease progression (a)	3 (3.9)	1 (2.0)
RECIST-defined disease progression (a)	74 (96.1)	50 (98.0)
Number of censored subjects	52 (40.3)	18 (26.1)
Reasons for censoring (b)		
Censored due to death after two or more missing tumor evaluations	3 (5.8)	0
No post-baseline tumor evaluation and no occurrence of death during the two tumor evaluation visits after randomization	4 (7.7)	7 (38.9)
Start of new anti-tumor treatment before disease progression or death	8 (15.4)	1 (5.6)
No event persisted as of the time of analysis, and the patient was known to have survived and had no RECIST progression as of the data cut-off date.	36 (69.2)	6 (33.3)
Withdrawal of informed consent before disease progression or death	1 (1.9)	4 (22.2)

Table 10 PFS Analysis Results (BIIRC's Evaluation) - ITT Set

	Sulfatinib Arm (N=129)	Placebo Arm (N=69)
Number of subjects involved in PFS events	80 (62.0)	41 (59.4)
Death, no RECIST-defined disease progression (a)	1 (1.3)	0
RECIST-defined disease progression	79 (98.8)	41 (100.0)
Number of censored subjects	49 (38.0)	28 (40.6)
Reasons for censoring (b)		
Censored due to death after two or more missing tumor evaluations	5 (10.2)	
No baseline tumor evaluation	5 (10.2)	6 (21.4)
No post-baseline tumor evaluation and no occurrence of death during the two tumor evaluation visits after randomization	0	1 (3.6)
Start of new anti-tumor treatment before disease progression or death	7 (14.3)	4 (14.3)
No event persisted as of the time of analysis, and the patient was known to have survived and had no RECIST progression as of the data cut-off date.	31 (63.3)	13 (46.4)
Withdrawal of informed consent form before disease progression or death	1 (2.0)	4 (14.3)

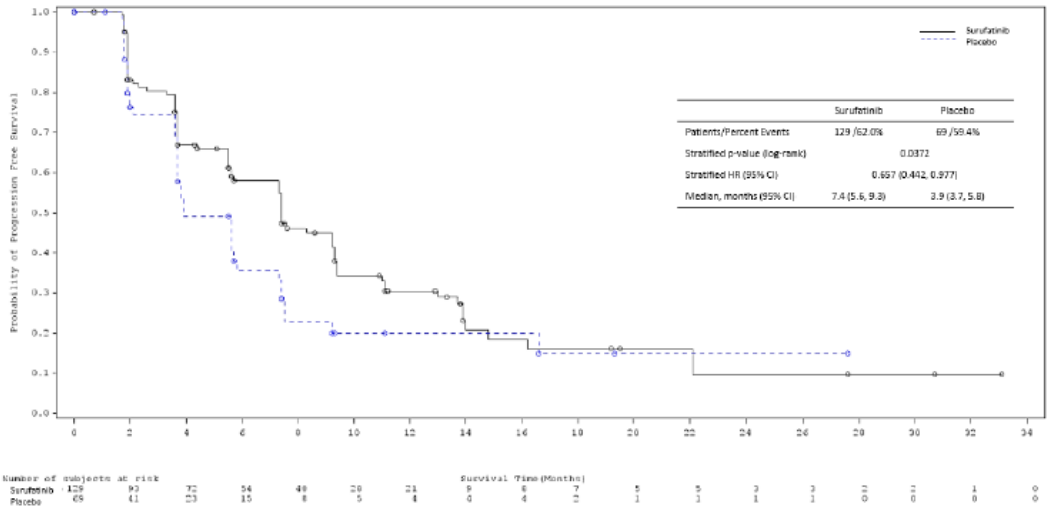
Figure 17. Kaplan-Meier Plot for Investigator-Assessed PFS Analysis (Primary Endpoint) – ITT set (Study 2015-012-00CH4)



CI=confidence interval; CSR=clinical study report; HR=hazard ratio; ITT=intent-to-treat; PFS=progression-free survival

Source: Figure 14.2.1.1.1 and Table 14.2.1.1 from the Study 2015-012-00CH4 CSR

Figure 18. Kaplan-Meier Plot for BIIRC-Assessed PFS Analysis (Supportive Analysis) – ITT Set (Study 2015-012-00CH4)



BIIRC=Blinded Independent Image Review Committee; CI=confidence interval; CSR=clinical study report; HR=hazard ratio; ITT= intent-to-treat; PFS=progression-free survival.
Source: Figure 14.2.1.3.1 from the Study 2015-012-00CH4 CSR

Table 16. Discordance of PFS Between Investigator Assessment and BIIRC Assessment – ITT Set (Study 2015-012-00CH4)

	Surufatinib (N=129)	Placebo (N=69)
Progression or death by Investigator, n (%)		
n	77	51
PD or Death by BIIRC	62 (48.1)	41 (59.4)
Censored by BIIRC	15 (11.6)	10 (14.5)
Censored by Investigator, n (%)		
n	52	18
Censored by BIIRC	34 (26.4)	18 (26.1)
PD or Death by BIIRC	18 (14.0)	0
Event concordance rate, %[a]	**74.4**	**85.5**

BIIRC= Blinded Independent Image Review Committee; ITT= intent-to-treat; PD= Progressive disease.
[a] Proportion of patients with PD, death, or censored by both Investigator and BIIRC.
Source: Table 14.2.1.11 from the Study 2015-012-00CH4 CSR

According to the SAP, an estimated median PFS of 8 months was anticipated for the control arm in SANET-ep. The patients in the control arm did notably worse, which is worrisome considering their relatively young age, early treatment setting (one third of patients without prior systemic therapy), and good status (low ECOG PS) of the majority. Distribution of KI-67 does not explain this difference. The shorter than anticipated PFS times cast concern over generalisability of the study results in the general disease population.

Secondary endpoints – ORR and DCT in i-ITT at interim analysis 31-MAR-2019:

Table 17. ORR and DCT in i-ITT

	Investigator-Assessed		BIIRC-Assessed	
	Surufatinib (N=126)	**Placebo (N=64)**	**Surufatinib (N=126)**	**Placebo (N=64)**
Unconfirmed ORR (CR+PR), n (%)[a,b]	**13 (10.3)**	**0**	**10 (7.9)**	**0**
95% exact CI	(5.6, 17.0)		(3.9, 14.1)	
Odds ratio (95% CI)	NE		NE	
p-value	0.0051		0.0174	
Confirmed ORR (CR+PR), n (%)[a,b]	**11 (8.7)**	**0**	**8 (6.3)**	**0**
95% exact CI	(4.4, 15.1)		(2.8, 12.1)	
Odds ratio (95% CI)	NE		NE	
p-value	0.0171		0.0532	
DCR (CR+PR+SD), n (%)[a,b]	**109 (86.5)**	**42 (65.6)**	**98 (77.8)**	**43 (67.2)**
95% exact CI	(79.3, 91.9)	(52.7, 77.1)	(69.5, 84.7)	(54.3, 78.4)
Odds ratio (95% CI)	3.3 (1.5, 7.3)		1.7 (0.8 , 3.5)	
p-value	0.0022		0.1869	

BIIRC=blinded independent image review committee; CI=confidence interval; CR=complete response; DCR=disease control rate; iITT=interim intent-to-treat; IWRS=interactive web response system; NE=not evaluable; ORR=objective response rate; PR=partial response; SD=stable disease.

Note: Fisher's exact test was used to compare the treatment differences of ORR, and the 95% exact CI of ORR was calculated using the exact method.

[a] For ORR and DCR, the 95% exact CI was calculated using the Clopper-Pearson method.

[b] The odds ratio, 95% exact CI and p-value of DCR were calculated using the Cochran-Mantel-Haenszel stratified exact test. Stratification factors included: NET pathological grade (Grade 1 and Grade 2), whether systemic antitumor drugs for advanced disease (yes,no) were received, and primary tumor sites (A+C, B). All stratification factors were collected from IWRS.

Source: Table 14.2.3.1 and Table 14.2.3.2 from the Study 2015-012-00CH4 and Table 14.2.3.3 and Table 14.2.3.4

Secondary endpoint – OS in ITT at updated analysis 30-OCT-2020:

Table 18. Overall Survival Analysis – ITT Set (Study 2015-012-00CH4)

	Surufatinib (N=146)	**Placebo (N=72)**
Deaths, n (%)	57 (39.0)	25 (34.7)
Median (95% CI) (months)[a]	38.7 (29.7, NE)	40.4 (29.1, NE)
Stratified HR (95% CI)[b, c]	1.143 (0.708, 1.845)	

CI=confidence interval; HR=hazard ratio; ITT= intent-to-treat; IWRS=interactive web response system; NE=not evaluable; NET=neuroendocrine tumor; SAP=statistical analysis plan.

Note: Only for patients randomized before 30 October 2020

[a] The Kaplan-Meier method was used. The 2-sided 95% CI was calculated based on the Brookmeyer and Crowley method.

[b] Based on stratified Cox proportional hazard regression model.

[c] The stratification factors are NET pathological grade (Grade 1 and Grade 2), previous systemic antitumor for advanced disease (yes, no), and primary lesion of tumor in A+C (jejunum, ileum, duodenum, thymus gland, caecum, and other origin or unknown origin) or B (lung, stomach, liver, appendix, colon, and rectum). All factors are per IWRS. The stratum was determined at the Blinded Data Review Meeting in accordance with SAP before interim analysis database.

Source: Table 14.2.2.1.1.2

Table 19. Summary of Deaths – Safety Set (Study 2015-012-00CH4)

	Surufatinib (N=144)	Placebo (N=72)
Number of patients treated	**144**	**72**
Double-blind phase, n (%)		
Number of patients who died	3 (2.1)	2 (2.8)
Primary cause of death		
Disseminated intravascular coagulation and hepatic encephalopathy	1 (0.7)	0
Liver injury	1 (0.7)	0
Progression of disease	0	1 (1.4)
Respiratory failure and late cancer cachexia	0	1 (1.4)
Unknown	1 (0.7)	0
Open-label phase, n (%)		
Number of patients who died	1 (0.7)	2 (2.8)
Primary cause of death		
Progression of disease	1 (0.7)	2 (2.8)
Survival follow-up period, n (%)		
Number of patients who died	53 (36.8)	21 (29.2)
Primary cause of death		
Hypoglycemia	1 (0.7)	0
Progression of disease	28 (19.4)	12 (16.7)
Unknown	23 (16.0)	8 (11.1)
Missing	1 (0.7)	1 (1.4)

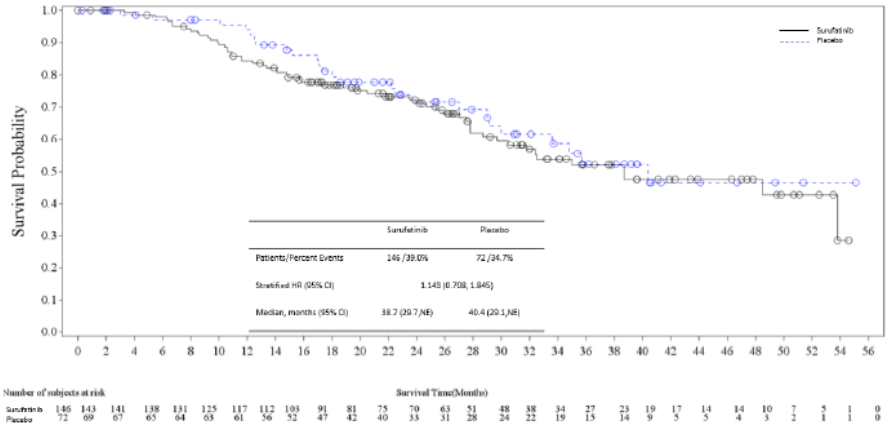
ITT= intent-to-treat.
Note: Two patients in the surufatinib arm were randomized but not treated.
Percentages were calculated based on number of patients treated.
Source: Table 14.3.2.1.7.1

Table 20. Overall Survival Exploratory Analysis – ITT Set (Study 2015-012-00CH4)

	Surufatinib	Placebo
Time-dependent covariate		
Stratified HR (95% CI)	0.969 (0.489, 1.923)	
Censor placebo at the time of crossover		
Deaths, n (%)	57 (39.0)	10 (13.9)
Median (95% CI) (months)	38.7 (29.7, NE)	33.6 (22.2, NE)
Stratified HR (95% CI)	1.004 (0.501, 2.013)	
RPSFT		
N	146	72
Deaths, n (%)	57 (39.0)	24 (33.3)
Median (95% CI) (months)	38.7 (29.7, NE)	44.9 (33.1, NE)
Stratified HR (95% CI)	1.269 (0.778, 2.070)	

CI=confidence interval; HR=hazard ratio; ITT= intent-to-treat; NE=not evaluable; RPSFT=rank-preserving structural failure time.
Note: HR <1 indicates survival benefit in surufatinib arm.
Source: Table 14.2.2.1.2.2, Table 14.2.2.1.3.2, and Table 14.2.2.1.4.2

Figure 19. Kaplan-Meier Plot for OS (Surufatinib Versus Placebo) – ITT Set (Study 2015-012-00CH4)



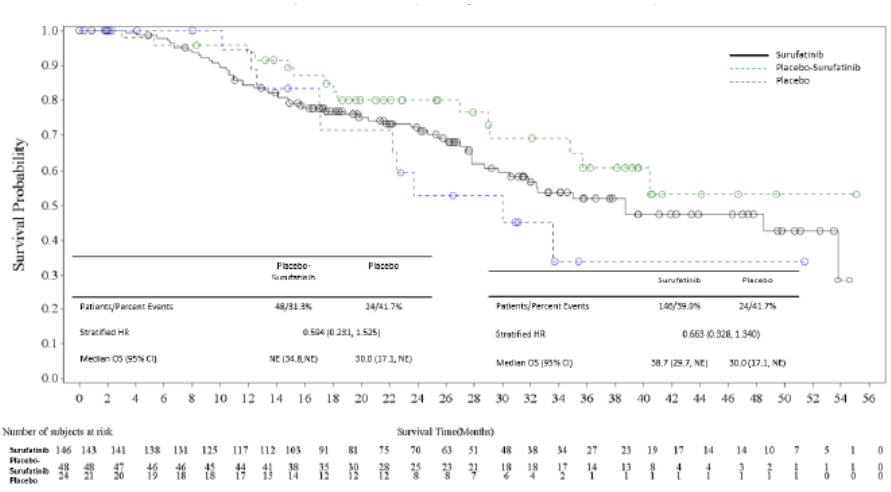
CI=confidence interval; HR=hazard ratio; ITT= intent-to-treat; OS=overall survival.
Note: Only for patients randomized before 30 October 2020.
Source: Figure 14.2.1.1.1.3

Table 21. Analysis of OS (Surufatinib Versus Placebo; Placebo-Surufatinib Versus Placebo) – ITT Set (study 2015-012-00CH4)

	Surufatinib (N=146)	Placebo-Surufatinib (N=48)	Placebo (N=24)
Deaths, n (%)	57 (39.0)	15 (31.3)	10 (41.7)
Median (months)	38.7 (29.7, NE)	NE (34.8, NE)	30.0 (17.1, NE)
Stratified HR (95% CI) (Reference group: placebo)	0.663 (0.328, 1.340)	0.594 (0.231, 1.525)	

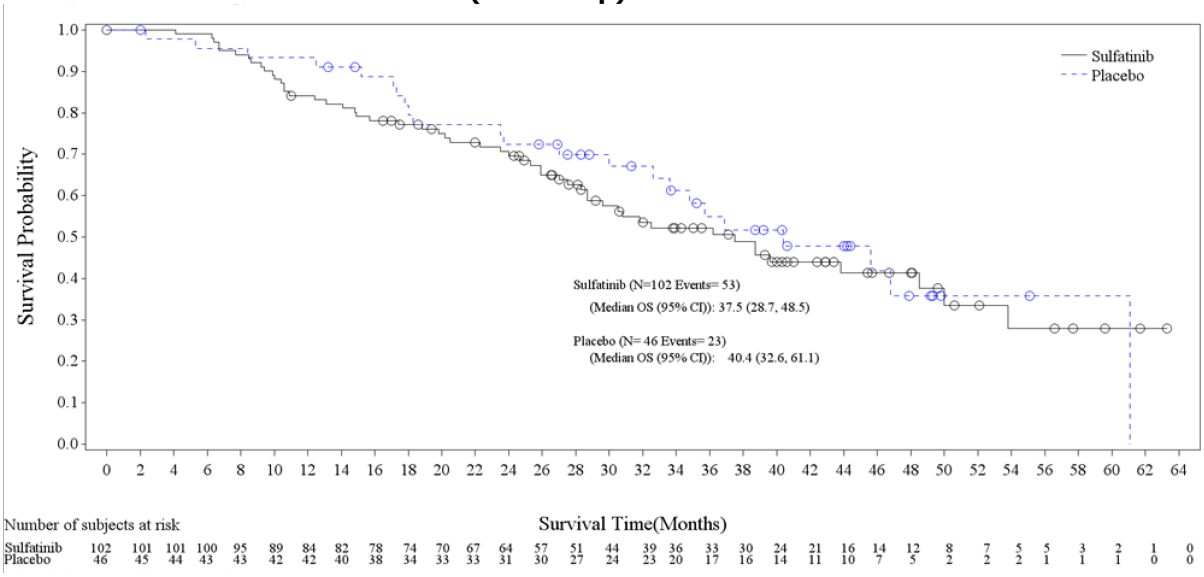
CI=confidence interval; HR=hazard ratio; ITT= intent-to-treat; NE=not evaluable; OS=overall survival.
Source: Table 14.2.2.1.5.2

Figure 20. Kaplan-Meier Plot for OS (Surufatinib Versus Placebo; Placebo-Surufatinib Versus Placebo) – ITT Set (Study 2015-012-00CH4)



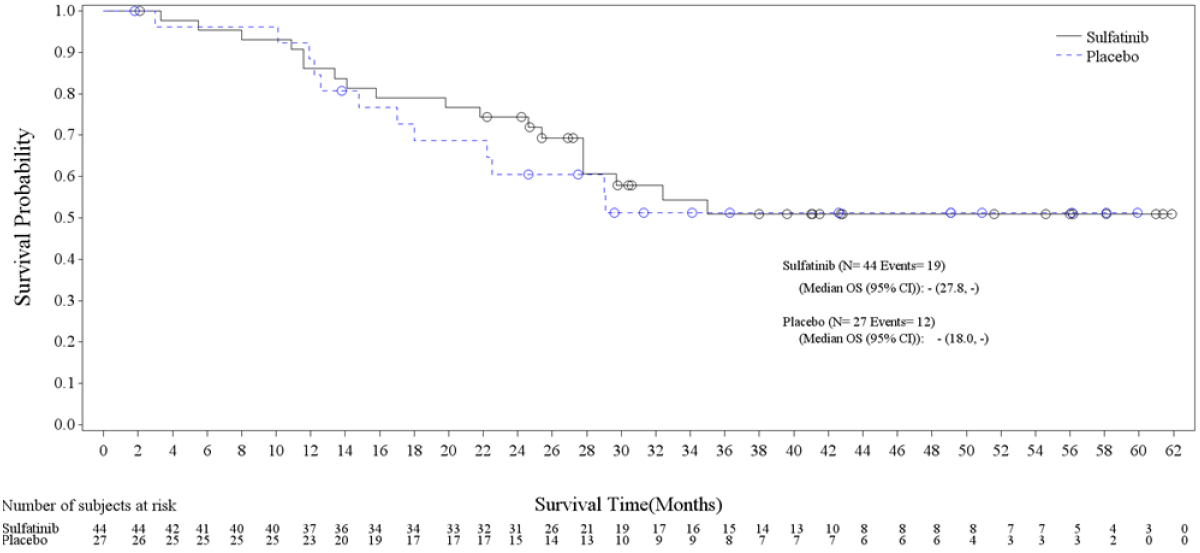
CI=confidence interval; HR=hazard ratio; ITT= intent-to-treat; NE=not evaluable; OS=overall survival.
Note: Only for patients randomized before 30 October 2020.
Source: Figure 14.2.1.1.1.4

Figure 21. Kaplan-Meier Curve of Overall Survival by Previous Systemic Anti-tumor Drug for Advanced Disease – Yes – ITT Set (SANET-ep)



Source: Figure 14.2.1.1.4.1, Study 2015-012-00CH4

Figure 22. Kaplan-Meier Curve of Overall Survival by Previous Systemic Anti-tumor Drug for Advanced Disease – No – ITT Set (SANET-ep)



Source: Figure 14.2.1.1.4.1, Study 2015-012-00CH4

Ancillary analyses

Sensitivity analyses:

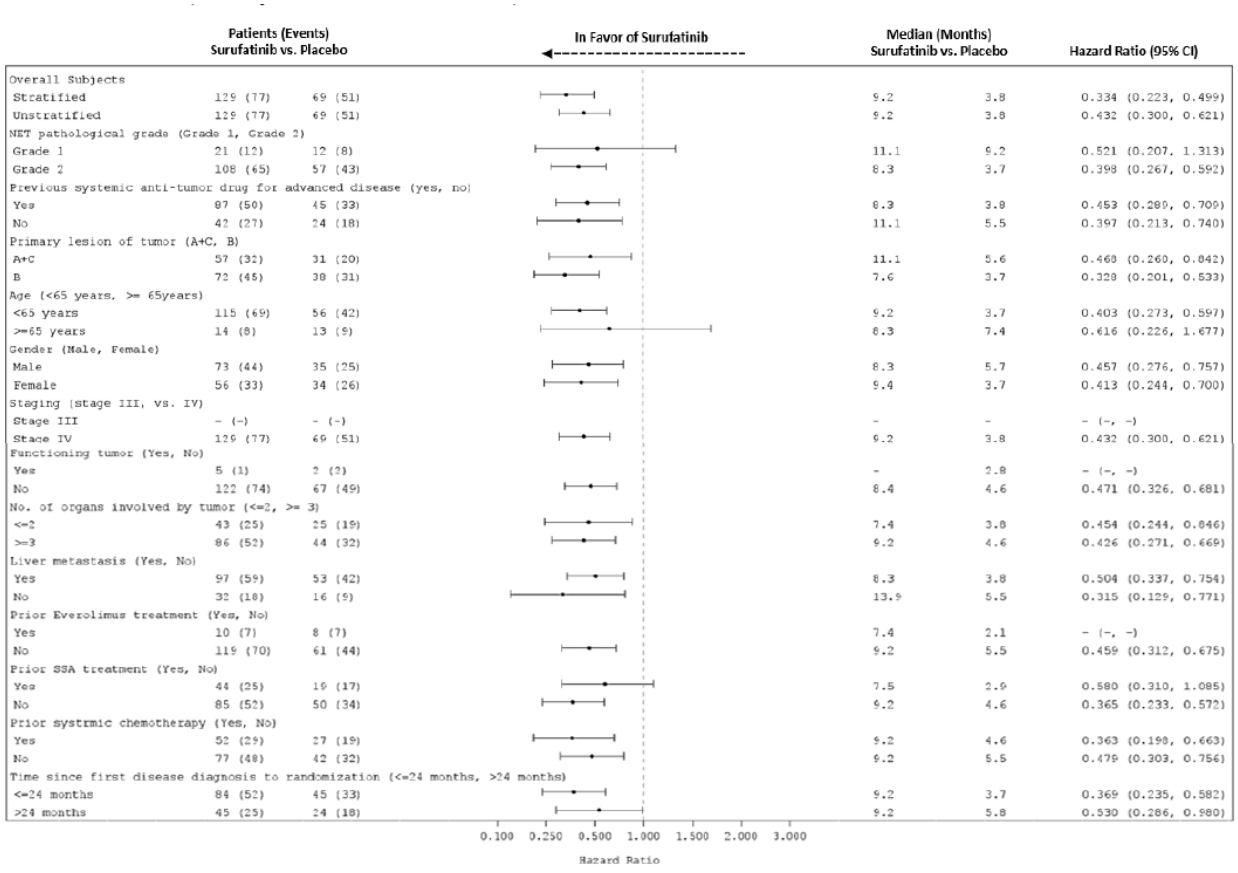
Table 22. Sensitivity Analyses of Investigator-Assessed PFS (study 2015-012-00CH4)

Progression-Free Survival	HR (95% CI)	p-value
Primary analysis-ITT set	0.334 (0.223, 0.499)	<0.0001
Sensitivity analyses		
PP set	0.325 (0.217, 0.486)	<0.0001
Treating progression/death after missed visits as progression at the next scheduled visit (ITT Set)	0.349 (0.235, 0.519)	<0.0001
Using CRF stratification factors or from independent pathology review (ITT Set)	0.338 (0.225, 0.505)	<0.0001
Unstratified analysis (ITT Set)	0.432 (0.300, 0.621)	<0.0001
Multivariate analysis, adjusting for potential prognostic factors (exploratory analysis; ITT Set)	0.409 (0.3, 0.6)	<0.0001

CRF=case report form; CSR=clinical study report; HR=hazard ratio; ITT= intent-to-treat; PFS=progression-free survival; PP=per protocol.
Source: Table 14.2.1.1, Table 14.2.1.2, Table 14.2.1.4, Table 14.2.1.5, Table 14.2.1.6, and Table 14.2.1.9 from the Study 2015-012-00CH4 CSR

Subgroup analyses:

Figure 23. Forest Plot for Subgroup Analysis of PFS (Investigator-Assessed) – ITT Set (Study 2015-012-00CH4)



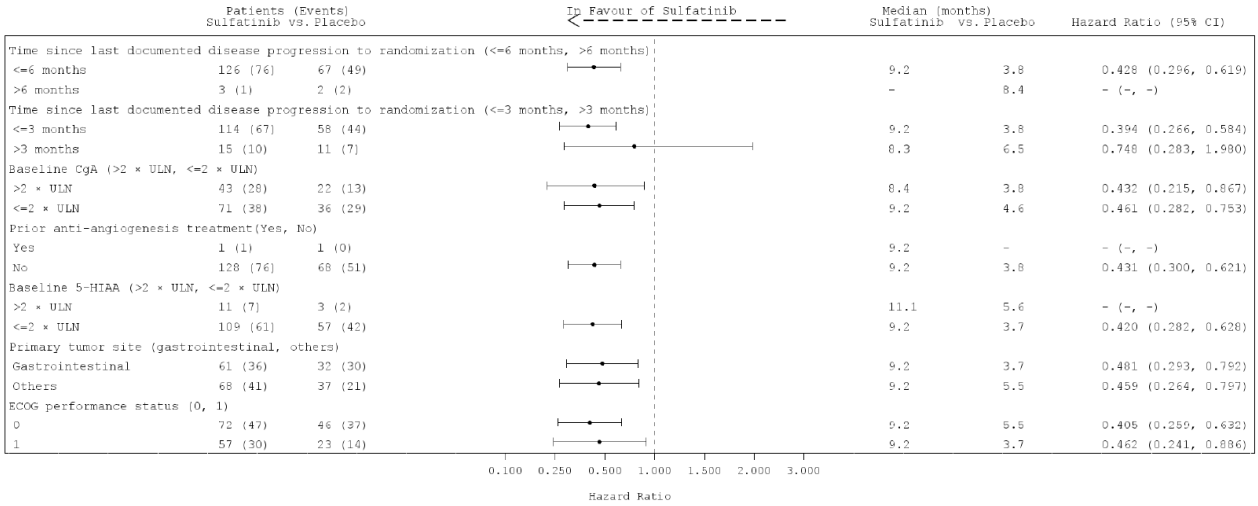
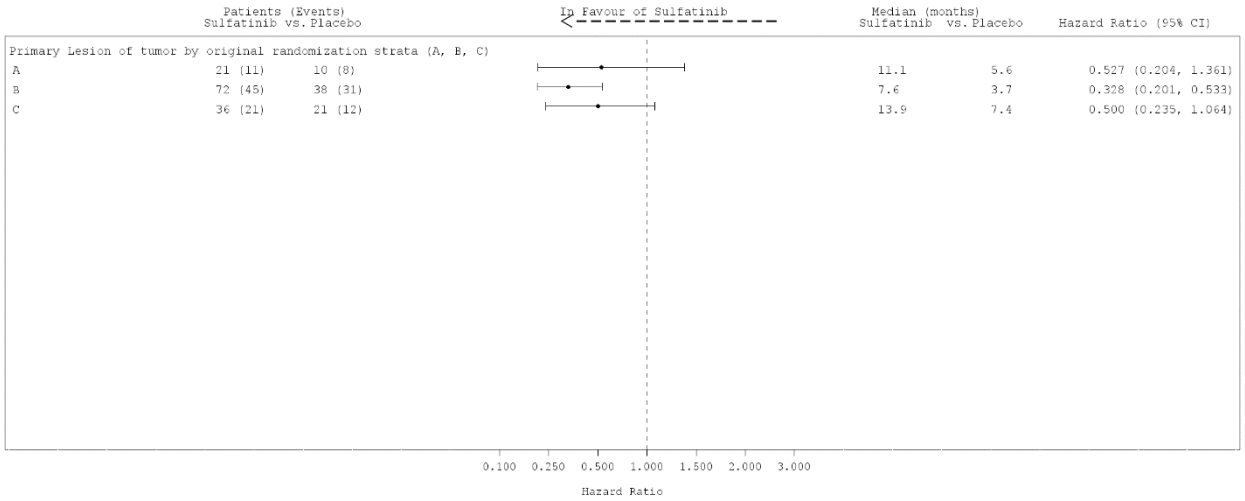


Figure 24. Forest Plot for Subgroup Analysis of Progression Free Survival for Original Randomization Strata (A, B, C)

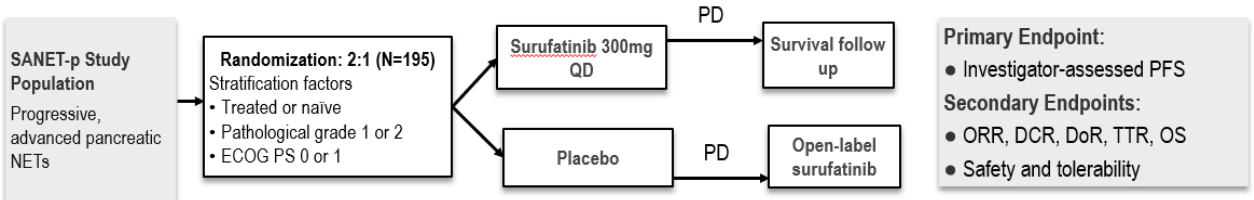


Source: Figure 14.2.1.7.4.1, Study 2015-012-00CH4
A = jejunum, ileum, duodenum, thymus, cecum; B = lung, liver, stomach, appendix, colon, rectum; C = other or unknown origins

2015-012-00CH3 (SANET-p)

Study 2015-012-00CH3 (SANET-p) is a randomized, double-blind, placebo-controlled, multicentre, phase 3 clinical study to assess the efficacy and safety of surufatinib monotherapy in patients with advanced pNETs. An overview of the study design is provided in Figure RT.

Figure 25. Study design of SANET-p



Methods

Study Participants

The target population was patients with progressive unresectable locally advanced or distant metastatic, low- and intermediate-grade pNET (G1 or G2).

The inclusion and exclusion criteria from SANET-p were identical to those of SANET-ep, with the obvious exception of pancreatic NETs instead of extrapancreatic NETs.

Treatments

Identical as those from SANET-ep, described previously.

Objectives

Identical as those from SANET-ep, described previously.

Outcomes/endpoints

Identical as those from SANET-ep, described previously.

Sample size

The calculation of sample size was based on the following assumptions:

- The total two-tailed significance level is 0.05;
- The median PFS of the control arm is 6 months;
- The hazard ratio (HR) of the trial arm to the control arm is 0.55 based on a statistical power of approximately 89%;
- The enrollment rate is approximately 10 subjects per month;
- The 24-month dropout rate is approximately 20%;
- The randomization ratio is 2:1;
- Interim analysis is conducted after obtaining 92 (70%) of the expected PFS events, and the O'Brien-Fleming boundary shape method is used to conduct α control.

Under the premise of these assumptions, this study planned to recruit 195 subjects within 20 months, and 131 PFS events were observed 7 months after the end of enrollment.

Randomisation and blinding (masking)

About 195 subjects were randomized (according to the ratio of 2:1) to the following treatment arms based on the IWRS:

- Surufatinib 300 mg QD
- Placebo 300 mg QD

The randomization stratification factors were: NET pathological grade (G1 or G2), prior systemic anti-tumour treatment (yes or no) and Eastern Cooperative Oncology Group (0,1).

Regarding blinding, it was identical as that from SANET-ep, described previously.

Statistical methods

Analysis sets:

Identical as those from SANET-ep, described previously.

Primary and secondary endpoints, sensitivity analyses:

Identical as those from SANET-ep, described previously.

Multiplicity adjustment and interim analysis:

An interim analysis, that allows for stopping the study for superior efficacy is planned when approximately 92 (70%) of the PFS events have been documented in the ITT population. An α-spending function due to Lan DeMets (1983) with O' Brien-Fleming type stopping boundary (as implemented in EAST 6.3) will be used for the interim efficacy analysis. Therefore, if the interim analysis is performed exactly after 92 events have been documented, a nominal p-value of less than 0.015 (corresponding to an upper bound of hazard ratio = 0.584) will need to be observed to declare statistical significance.

Changes to the planned analyses:

The following analysis sets were included in the SAP, but were not included in the protocol:

Open-label study analysis set

iITT set

Full subject set

The following analysis and study endpoints were included in the SAP, but were not included in the protocol:

The exploratory analysis on the possible effects of baseline covariate on the primary study endpoint (PFS).

The confirmed ORR, DOR, DCR and TTR.

The best change of target lesion was added as a secondary efficacy endpoint, and a description on the corresponding analysis method was provided.

Changes in the statistical analysis method relative to the protocol:

- The 95% CI of the DCR and ORR treatment difference was calculated using the exact method instead of the normal approximation method.
- As exploratory analyses, EORTC QLQ-C30 and QLQ-CI.NET21 only provided descriptive statistics.

Results

Participant flow

Figure 26. Participant flow from SANET-p, all subjects

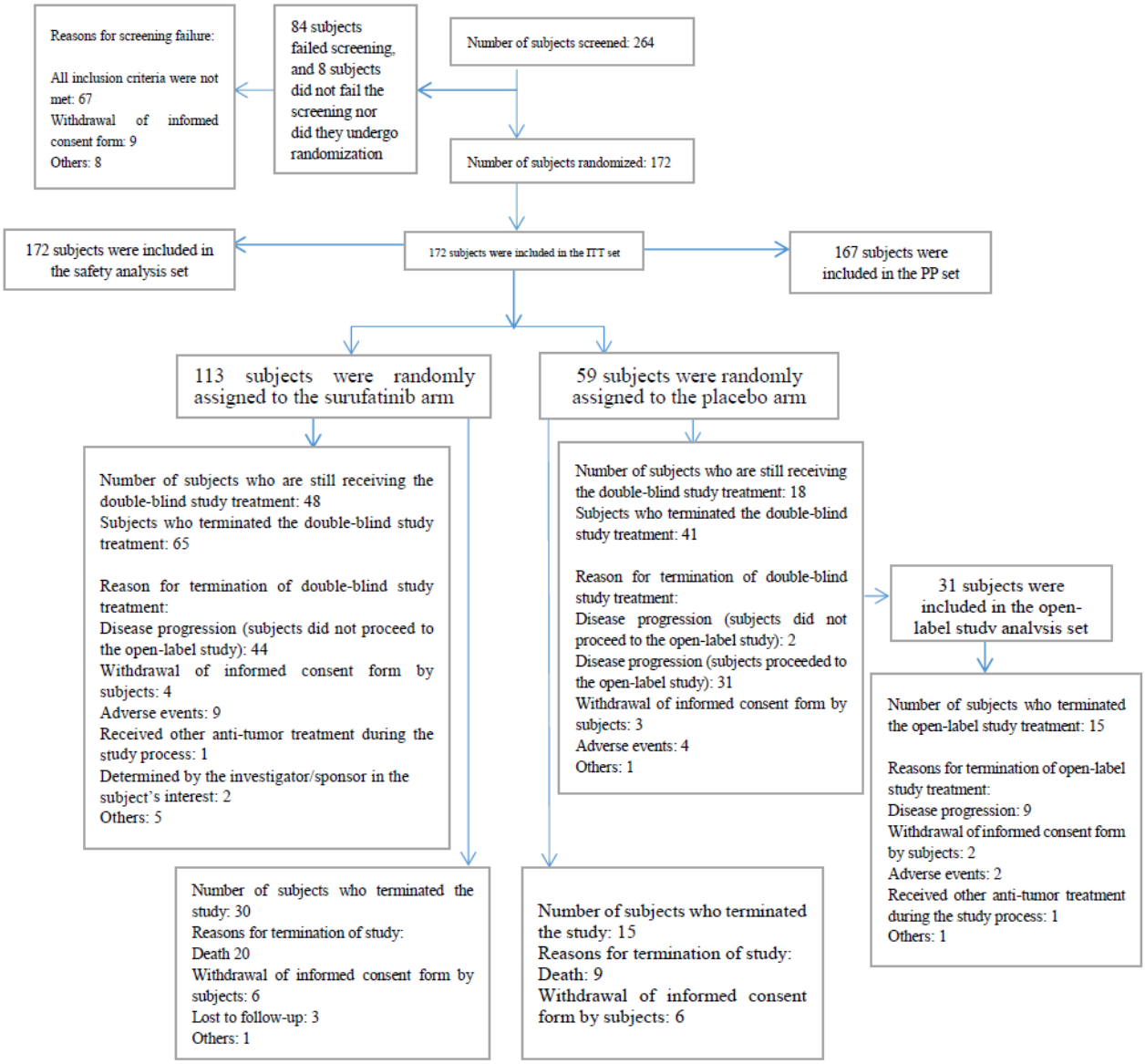


Table 23. Patient disposition from SANET-p, all subjects

Description	Surufatinib Arm n (%)	Placebo Arm n (%)	Total n (%)
Number of subjects screened			264
Screening failure			84
Reasons for screening failure			
All inclusion criteria were not met			67
Withdrawal of informed consent form			9
Others			8
Number of subjects randomized (a)	113	59	172 (65.2)
Number of subjects who received treatment (b)	113 (100.0)	59 (100.0)	172 (100.0)
Number of subjects who are still receiving the double-blind study treatment (c)	48 (42.5)	18 (30.5)	66 (38.4)
Number of subjects who terminated the double-blind study treatment (c)	65 (57.5)	41 (69.5)	106 (61.6)
Reason for termination of double-blind study treatment:			
PD (subjects did not enter the open-label study)	44 (38.9)	2 (3.4)	46 (26.7)
PD (subjects entered the open-label study)	0	31 (52.5)	31 (18.0)
Adverse Events	9 (8.0)	4 (6.8)	13 (7.6)
Withdrawal of informed consent form by subjects	4 (3.5)	3 (5.1)	7 (4.1)
Others	5 (4.4)	1 (1.7)	6 (3.5)
Determined by the investigator/sponsor in the subject's interest	2 (1.8)	0	2 (1.2)
Received other anti-tumor treatment during the study process	1 (0.9)	0	1 (0.6)
Death	0	0	0
Poor compliance	0	0	0
Pregnancy	0	0	0
Lost to follow-up	0	0	0
Number of subjects who terminated the open-label study treatment (d)		15 (48.4)	15 (48.4)
Reasons for termination of open-label study treatment			
PD		9 (29.0)	9 (29.0)
Withdrawal of informed consent form by subjects		2 (6.5)	2 (6.5)
Adverse Events		2 (6.5)	2 (6.5)
Received other anti-tumor treatment during the study process		1 (3.2)	1 (3.2)
Others		1 (3.2)	1 (3.2)
Death		0	0
Pregnancy		0	0
Lost to follow-up		0	0
Determined by the investigator/sponsor in the subject's interest		0	0
Number of subjects who terminated the study (b)	30 (26.5)	15 (25.4)	45 (26.2)
Reasons for termination of study			
Death	20 (17.7)	9 (15.3)	29 (16.9)
Withdrawal of informed consent form by subjects	6 (5.3)	6 (10.2)	12 (7.0)
Lost to follow-up	3 (2.7)	0	3 (1.7)
Others	1 (0.9)	0	1 (0.6)
Poor compliance	0	0	0
Termination of study by sponsor	0	0	0

Source: Statistical Table 14.1.1.1

Abbreviations: PD = progressive disease.

(a) Percentage based on the number of subjects screened.

(b) Percentage based on the number of subjects randomized.

(c) Percentage based on the number of subjects who received treatment.

(d) Percentage based on the number of subjects who entered the open-label study treatment due to PD.

Eight subjects are still in the screening period. The subjects did not fail the screening nor did they proceed to the randomization stage.

Protocol deviations:

Table 14.1.1.3 Summary of Major Protocol Deviations during Double Blind Treatment Phase – ITT Set

Site: Overall

	Sulfatinib (N = 113) n (%)	Placebo (N = 59) n (%)	Total (N = 172) n (%)
At least one major protocol deviation	12 (10.6)	2 (3.4)	14 (8.1)
Inclusion / Exclusion	2 (1.8)	2 (3.4)	4 (2.3)
Informed Consent Deviations	1 (0.9)	0	1 (0.6)
Other	2 (1.8)	0	2 (1.2)
Procedures / Tests	1 (0.9)	0	1 (0.6)
Prohibit Medication	4 (3.5)	0	4 (2.3)
Study Drug	3 (2.7)	0	3 (1.7)

This table include all major protocol deviations that are identified and determined at Blinded Data Review Meeting. Not all major protocol deviations lead to exclusion of subjects from per-protocol set unless they may affect efficacy evaluation.

Recruitment

First patient randomised (signing IC): 18-FEB-2016

Primary PFS analysis (data cut-off date): 11-NOV-2019

Last patient randomised: 16-DEC-2019

iDMC disclosure of interim analysis results: 20-JAN-2020

Study unblinding (termination of study): 07-FEB-2020

OS update (data cut-off date): 20-OCT-2020

At interim analysis of PFS, performed on 11-NOV-2019, the median duration of follow-up (time from date of randomization to date of PD/death or censoring using reverse Kaplan-Meier methodology) was 19.3 months (95% CI: 9.3, 19.4) in the surufatinib arm and 11.1 months (95% CI: 5.7, 35.9) in the placebo arm.

At updated OS analysis, performed on 30-OCT-2020, the median follow-up time was 28.3 months (95% CI: 21.6, 32.7) in the surufatinib arm and 28.1 months (95% CI: 22.9, 37.6) in the placebo arm.

Duration of follow-up up to primary PFS analysis was not balanced between arms, with surufatinib almost doubling that of placebo (19 vs 11 months). A "reverse" Kaplan-Meier curve was presented to investigate whether the censoring pattern differ between the two arms. No relevant differences are observed in the censoring pattern between the arms up to the first 10-12 months. After 12 months, the number of patients at risk of being censored in the placebo arm is 6 compared to 25 in the active arm.

Conduct of the study

The study protocol was revised twice in total during this study period, with the latest version as 3.0 (version date 19-OCT-2017).

Main changes implemented in Protocol Amendment 1 (02-NOV-2016, Version 2.0):

The provisions on the past anti-tumor drug treatment regimens of the target population were revised. The requirements on liver function status at baseline were revised. The requirements on QT interval of ECG examination at baseline were revised.

The dose adjustment strategy and adverse reaction management of surufatinib were revised in accordance with the management experience of adverse reactions in the phase Ib/II study of surufatinib in patients with NET.

Observation data and management recommendations for hypertension were added.

The part on "patients who did not experience PD at the end of the double-blind study treatment should continue to undergo tumor evaluation based on the protocol until he/she experiences PD determined by BIIRC" was revised.

The requirements on termination of treatment by patients in the double-blind treatment phase was revised. Additional requirements and procedures for the end-of-double-blind treatment visit were added for patients who are about to be unblinded. A description on the follow-up period was supplemented.

Additional requirements and procedures were added for unblinding after PD determined by BIIRC (Blinded Independent Image Review Committee).

Additional requirements and procedures were added for the open-label study phase.

A description on the determination of sample size and statistical calculation process of the analysis plan was provided.

Main changes implemented in Protocol Amendment 3 (19-OCT-2017, Version 3.0):

The error in the number of study sites was corrected.

A description was added to state that patients who are still receiving surufatinib treatment after unblinding of the entire study shall roll over to another open-label study and receive the surufatinib treatment. A clarification on the requirements for entering the open-label study phase was provided.

The statistical analysis of the primary study endpoint was mainly revised based on the tumor evaluation data determined by the investigator, and the tumor evaluation data of the BIIRC was used as the supporting analysis.

The data for the phase Ib/II NET study on surufatinib was updated.

Baseline data

Table 24. Patient demographics and baseline characteristics – ITT set study SANET-p

Characteristics	Surufatinib Arm (N = 113)	Placebo Arm (N = 59)	Total (N = 172)
Age (years)			
n	113	59	172
Mean (standard deviation)	50.24 (11.116)	49.29 (13.395)	49.91 (11.916)
Median	51.00	48.00	50.00
Minimum, maximum	25.0, 75.0	20.0, 77.0	20.0, 77.0
Age group, n (%)			
< 65 years old	97 (85.8)	52 (88.1)	149 (86.6)
≥ 65 years old	16 (14.2)	7 (11.9)	23 (13.4)
Gender, n (%)			
Male	60 (53.1)	28 (47.5)	88 (51.2)
Female	53 (46.9)	31 (52.5)	84 (48.8)
Whether the subject is of childbearing age			
Yes	23 (43.4)	21 (67.7)	44 (52.4)
No	30 (56.6)	10 (32.3)	40 (47.6)
Race, n (%)			
Asian	113 (100.0)	59 (100.0)	172 (100.0)
Chinese	113 (100.0)	59 (100.0)	172 (100.0)
Whether the subject smokes, n%			
Never	78 (69.0)	46 (78.0)	124 (72.1)
Yes	10 (8.8)	2 (3.4)	12 (7.0)
Previously smoked	25 (22.1)	11 (18.6)	36 (20.9)
Whether the subject consumes alcohol, n%			
Never	81 (71.7)	46 (78.0)	127 (73.8)
Yes	10 (8.8)	1 (1.7)	11 (6.4)
Previously consumed alcohol	22 (19.5)	12 (20.3)	34 (19.8)
Height (cm)			
n	113	58	171
Mean (standard deviation)	165.87 (7.994)	164.76 (7.930)	165.49 (7.966)
Median	165.00	166.50	166.00
Minimum, maximum	148.0, 186.0	144.0, 179.0	144.0, 186.0
No data available	0	1	1
Body weight (kg)			
n	113	59	172
Mean (standard deviation)	63.07 (10.772)	59.37 (11.925)	61.80 (11.284)
Median	63.00	58.00	60.40
Minimum, maximum	40.0, 90.0	39.5, 95.0	39.5, 95.0
BMI (kg/m^2)			
n	113	58	171
Mean (standard deviation)	22.85 (3.065)	21.78 (3.431)	22.49 (3.224)
Median	22.70	21.65	22.30
Minimum, maximum	16.4, 30.1	15.2, 34.9	15.2, 34.9

Table 25. Baseline tumour characteristics – ITT set study SANET-p

Characteristics	Surufatinib Arm (N = 113)	Placebo Arm (N = 59)	Total (N = 172)
Time interval between the first diagnosis and time of randomization (months)			
n	113	59	172
Mean (standard deviation)	28.71 (31.337)	28.21 (28.417)	28.54 (30.285)
Median	18.30	18.30	18.30
Minimum, maximum	0.8, 182.1	1.2, 127.3	0.8, 182.1
Time interval between the first diagnosis and time of randomization, n (%)			
≤ 24 months	67 (59.3)	36 (61.0)	103 (59.9)
> 24 months	46 (40.7)	23 (39.0)	69 (40.1)
Primary tumor site			
Pancreas	113 (100.0)	59 (100.0)	172 (100.0)
Others	0	0	0
Site pathological grade n, (%)			
G1	14 (12.4)	9 (15.3)	23 (13.4)
G2	99 (87.6)	50 (84.7)	149 (86.6)
Stage of disease, n (%)			
I	0	0	0
II	0	0	0
III	0	2 (3.4)	2 (1.2)
IV	113 (100.0)	57 (96.6)	170 (98.8)
Tumor metastatic sites, n (%)			
Liver	108 (95.6)	54 (91.5)	162 (94.2)
Lymph nodes	42 (37.2)	21 (35.6)	63 (36.6)
Lung	9 (8.0)	3 (5.1)	12 (7.0)
Bone	16 (14.2)	3 (5.1)	19 (11.0)
Brain	0	0	0
Others	24 (21.2)	8 (13.6)	32 (18.6)
Number of tumor-affected organs, n (%)			
≤ 2	51 (45.1)	34 (57.6)	85 (49.4)
≥ 3	62 (54.9)	25 (42.4)	87 (50.6)
NET functional status, n (%)			
Functional	11 (9.7)	3 (5.1)	14 (8.1)
Non-functional	102 (90.3)	55 (93.2)	157 (91.3)
Unknown	0	1 (1.7)	1 (0.6)
Time interval between the last PD before enrollment to randomization (months)			
n	113	59	172
Mean (standard deviation)	1.56 (1.231)	1.52 (1.486)	1.54 (1.320)
Median	1.20	1.10	1.20
Minimum, maximum	0.0, 6.8	0.1, 10.6	0.0, 10.6
≤ 6 months	111 (98.2)	58 (98.3)	169 (98.3)
> 6 months	2 (1.8)	1 (1.7)	3 (1.7)
≤ 3 months	102 (90.3)	54 (91.5)	156 (90.7)
> 3 months	11 (9.7)	5 (8.5)	16 (9.3)
ECOG PS, n (%)			
0	73 (64.6)	43 (72.9)	116 (67.4)
1	40 (35.4)	16 (27.1)	56 (32.6)
Baseline CgA, µg/L			
n	103	55	158
Mean (standard deviation)	1159.15 (4479.906)	1743.07 (6359.697)	1362.41 (5198.842)
Median	161.61	148.75	156.45
Minimum, maximum	20.1, 42995.0	20.6, 46140.0	20.1, 46140.0
Missing	10	4	14
> 2 × ULN	44 (38.9)	24 (40.7)	68 (39.5)
<= 2 × ULN	59 (52.2)	31 (52.5)	90 (52.3)
Received prior systemic anti-tumor drug therapy for advanced tumors, n (%)			
Yes	74 (65.5)	39 (66.1)	113 (65.7)
No	39 (34.5)	20 (33.9)	59 (34.3)
Received prior sunitinib therapy, n (%)			
Yes	4 (3.5)	6 (10.2)	10 (5.8)
No	109 (96.5)	53 (89.8)	162 (94.2)
Received prior everolimus therapy, n (%)			
Yes	12 (10.6)	4 (6.8)	16 (9.3)
No	101 (89.4)	55 (93.2)	156 (90.7)
Received prior somatostatin analog therapy, n (%)			
Yes	48 (42.5)	28 (47.5)	76 (44.2)
No	65 (57.5)	31 (52.5)	96 (55.8)
Prior systemic chemotherapy, n (%)			
Yes	33 (29.2)	12 (20.3)	45 (26.2)
No	80 (70.8)	47 (79.7)	127 (73.8)
Received prior antiangiogenic drug therapy, n (%)			
Yes	5 (4.4)	6 (10.2)	11 (6.4)
No	108 (95.6)	53 (89.8)	161 (93.6)

Source: Statistical Table 14.1.2.1
Abbreviations: CRF = Case Report Form, NET = Neuroendocrine Tumors, ECOG PS = Eastern Cooperative Oncology Group Performance Status Score.
Note: N = number of subjects of each treatment arm in the analysis set. n = number of subjects in a specific category.

It has been clarified that patients who progressed *during* anti-VEGF/VEGFR were excluded, implying selectivity for patients with implicitly better prognosis (those who received anti-VEGF/VEGFR at any point but did not progress during treatment were allowed to participate).

As is the case with SANET-ep trial, the internal distribution of G1 (13%) and G2 (87%) in SANET-p does not seem to reflect the much higher incidence of G1 NETs in clinical practice. Again, this has an impact on external validity of the results.

Numbers analysed

Table 26. Analysis datasets – SANET-p

	Surufatinib Arm n (%)	Placebo Arm n (%)	Total n (%)
Full subject set			264
Randomized and enrolled	113	59	172
Intention-to-treat analysis set (ITT set) [(a)(b)]	113 (100.0)	59 (100.0)	172 (100.0)
Per protocol analysis set (PP set) [(c)(d)]	109 (96.5)	58 (98.3)	167 (97.1)
Interim intention-to-treat analysis set (iITT set) [(d)(h)]	104 (92.0)	53 (89.8)	157 (91.3)
Safety analysis set [(a)(e)]	113 (100.0)	59 (100.0)	172 (100.0)
Open-label study analysis set [(f)(g)]	31 (52.5)		31 (52.5)

Source: Statistical Table 14.1.1.2

Note:

(a) Based on the number of subjects randomized.

(b) The ITT set includes all randomized and enrolled subjects.

(c) The PP set includes all subjects from the ITT set who are not involved in major protocol deviations that have an effect on the efficacy evaluation.

(d) Based on the ITT set.

(e) The safety analysis set includes all subjects who received at least one dose of the study drug in the double-blind phase.

(f) The open-label study analysis set includes subjects who received at least one dose of surufatinib treatment in the open-label study phase.

(g) The percentages were calculated based on the number of subjects from the placebo arm that was included in the ITT set in the double-blind phase.

(h) The iITT set includes subjects in the ITT set who met at least one of the following criteria: (1) have at least one evaluable tumor assessment after the randomized treatment (at least 6 weeks); (2) terminated the double-blind study treatment for any reason.

Outcomes and estimation

Primary endpoint – INV-assessed PFS in ITT at interim analysis 11-NOV-2019

	Investigator Assessed (Primary Endpoint)		BIIRC Assessed (Supportive Analysis)	
	Surufatinib (N=113)	Placebo (N=59)	Surufatinib (N=113)	Placebo (N=59)
Number of PFS events, n (%)	**56 (49.6)**	**39 (66.1)**	**40 (35.4)**	**36 (61.0)**
Death, no RECIST-defined PD[a]	2 (3.6)	2 (5.1)	2 (5.0)	1 (2.8)
RECIST-defined PD[a]	54 (96.4)	37 (94.9)	38 (95.0)	35 (97.2)
Number censored	57 (50.4%)	20 (33.9%)	73 (64.6)	23 (39.0)
PFS (months), median (95% CI)[b]	**10.9 (7.5, 13.8)**	**3.7 (2.8, 5.6)**	**13.9 (11.0, 24.9)**	**4.6 (3.6, 7.4)**
Stratified HR (95% CI)[c]	0.491 (0.319, 0.755)		0.339 (0.209, 0.549)	
p-value of stratified log-rank test[d]	0.0011		<0.0001	
PFS rate (95% CI)[e]				
6 months	67.1 (55.7, 76.2)	31.8 (19.3, 45.1)	80.4 (69.9, 87.6)	36.9 (22.5, 51.3)
12 months	42.1 (30.5, 53.2)	23.1 (11.8, 36.6)	55.8 (42.5, 67.2)	20.7 (8.6, 36.5)
18 months	22.9 (13.4, 33.9)	19.3 (8.6, 33.1)	37.9 (24.9, 50.9)	16.6 (5.8, 32.2)
24 months	22.9 (13.4, 33.9)	15.4 (5.8, 29.4)	37.9 (24.9, 50.9)	8.3 (1.6, 22.6)

BIIRC=Blinded Independent Image Review Committee; CI=confidence interval; CSR=clinical study report; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; ITT=intent-to-treat; NET=neuroendocrine tumor; PD=progressive disease; PFS=progression-free survival; PS=performance status; RECIST=Response Evaluation Criteria in Solid Tumors.

Note: PFS refers to the time interval from the date of randomization to the first recorded PD or death due to any reason.

[a] Percentages were calculated based on the number of events.

[b] The Kaplan-Meier method was used. The 2-sided 95% CI was calculated based on the Brookmeyer and Crowley method.

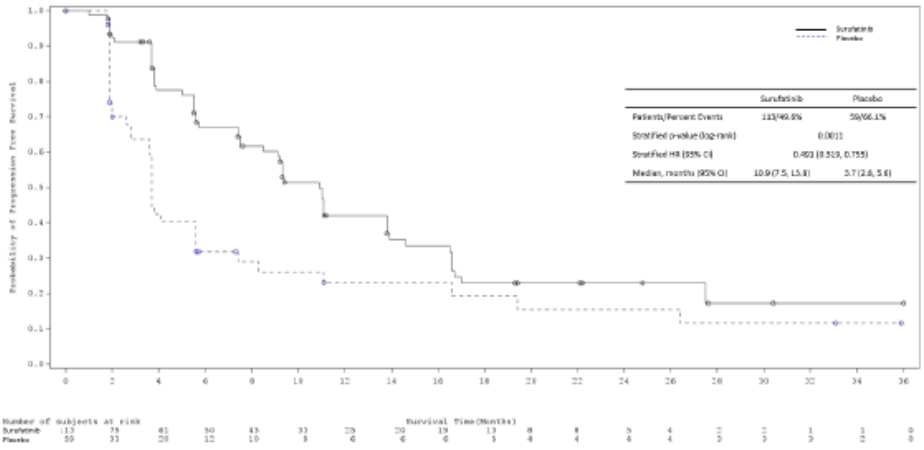
[c] The stratified Cox proportional hazard regression model was used for calculation. Stratification factors: NET pathological grade (G1 or G2), prior use of systemic antitumor drug treatment for advanced disease (yes or no), and ECOG PS (0, 1).

[d] The 2-sided stratified log-rank test was used. The stratification factors are the same as above.

[e] Calculated using Kaplan-Meier method and Greenwood formula for variance and log-log transformation.

Source: Table 14.2.1.1 and Table 14.2.1.3 from the Study 2015-012-00CH3 CSR

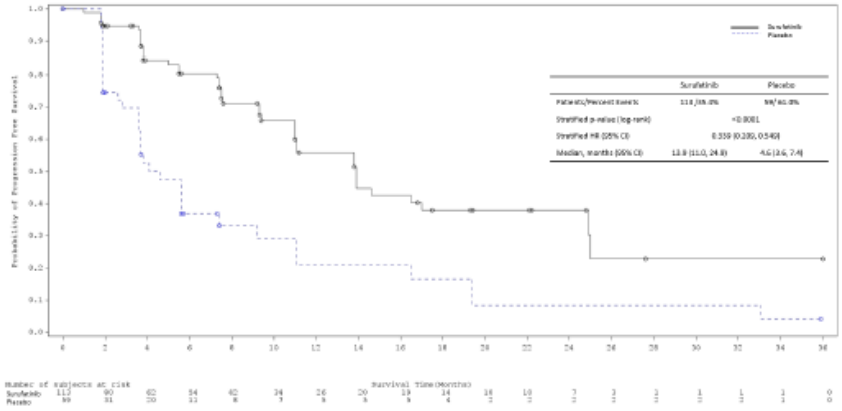
Figure 27. Kaplan-Meier Plot for Investigator-Assessed PFS Analysis (Primary Endpoint) – ITT Set (Study 2015-012-00CH3)



CI=confidence interval; CSR=clinical study report; HR=hazard ratio; ITT=intent-to-treat; PFS=progression-free survival.

Source: Figure 14.2.1.1.1 from the Study 2015-012-00CH3 CSR

Figure 28. Kaplan-Meier Plot for BIIRC-Assessed PFS Analysis (supportive Analysis) – ITT Set (Study 2015-012-00CH3)



BIIRC=Blinded Independent Image Review Committee; CI=confidence interval; CSR=clinical study report; HR=hazard ratio; ITT=intent-to-treat; PFS=progression-free survival.
Source: Figure 14.2.1.3.1 from the Study 2015-012-00CH3 CSR

Secondary endpoints – ORR and DCT in i-ITT at interim analysis 11-NOV-2019:

	Investigator Assessed		BIIRC Assessed	
	Surufatinib (N=104)	Placebo (N=53)	Surufatinib (N=104)	Placebo (N=53)
Unconfirmed ORR (CR+PR), n (%)[a,b]	20 (19.2)	1 (1.9)	15 (14.4)	1 (1.9)
95% exact CI	(12.2, 28.1)	(0.0, 10.1)	(8.3, 22.7)	(0.0, 10.1)
Odds ratio (95% CI)	12.4 (1.8 , 522.8)		8.8 (1.3 , 375.9)	
p-value	0.0021		0.0123	
Confirmed ORR (CR+PR), n (%)[a,b]	13 (12.5)	1 (1.9)	11 (10.6)	1 (1.9)
95% exact CI	(6.8, 20.4)	(0.0, 10.1)	(5.4, 18.1)	(0.0, 10.1)
Odds ratio (95% CI)	7.4 (1.0 , 321.7)		6.2 (0.8 , 269.7)	
p-value	0.0355		0.0609	
DCR (CR+PR+SD), n (%)[a,b]	84 (80.8)	35 (66.0)	88 (84.6)	36 (67.9)
95% exact CI	(71.9, 87.8)	(51.7, 78.5)	(76.2, 90.9)	(53.7, 80.1)
Odds ratio (95% CI)	2.1 (0.9, 4.8)		2.5 (1.1 , 6.1)	
p-value	0.0774		0.0311	

BIIRC=Blinded Independent Image Review Committee; CI=confidence interval; CR=complete response; CSR=clinical study report; DCR=disease control rate; ECOG= Eastern Cooperative Oncology Group; iITT=interim intent-to-treat analysis; IWRS=interactive web response system; NET=neuroendocrine tumor; ORR=objective response rate; PR=partial response; PS=performance status; SD=stable disease.

Note: Fisher's exact test was used to compare the treatment differences of ORR, and the 95% exact CI of ORR was calculated using the exact method.

[a] For ORR and DCR, the 95% exact CI was calculated using the Clopper-Pearson method.

[b] The odds ratio, 95% exact CI and p-value of DCR were calculated using the Cochran-Mantel-Haenszel stratified exact test. Stratification factors included the following: NET pathological grade, whether prior systemic antitumor drugs were received, and ECOG PS (0, 1). All stratification factors were collected from IWRS.

Source: Table 14.2.3.1, Table 14.2.3.2, Table 14.2.3.3, and Table 14.2.3.4 from the Study 2015-012-00CH3 CSR

Secondary endpoint – OS in ITT at updated analysis 30-OCT-2020:

Table 27. Overall Survival Analysis – ITT Set (Study 2015-012-00CH3)

	Surufatinib	Placebo
N	119	60
Deaths, n (%)	29 (24.4)	17 (28.3)
Median (95% CI) (months)[a]	NE (40.1, NE)	NE (26.4, NE)
Stratified HR (95% CI)[b]	0.846 (0.463, 1.545)	

CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; Gx=grade x; HR=hazard ratio; ITT=intent-to-treat; IWRS=interactive web response system; NE=not evaluable; NET=neuroendocrine tumor; OS=overall survival; PS=performance status.

Note: OS refers to the time interval from the date of randomization to death due to any reason.

[a] The Kaplan-Meier method was used. The 2-sided 95% CI was calculated based on the Brookmeyer and Crowley method.

[b] The stratified Cox proportional hazard model was used for calculation. Stratification factors: NET pathological grade (G1 or G2), prior use of systemic antitumor drug treatment (yes or no), and ECOG PS (0, 1). The information of stratification factors was collected based on IWRS.

Source: Table 14.2.2.1.1.2

Table 28. Overall Survival Exploratory Analysis – ITT Set (study 2015-012-00CH3)

	Surufatinib	Placebo
Time-dependent covariate		
Stratified HR (95% CI)[a, b]	0.729 (0.324, 1.637)	
Censor placebo at the time of crossover		
Deaths, n (%)	29 (24.4)	8 (13.3)
Median (95% CI) (months)[c]	NE (40.1, NE)	NE (22.5, NE)
Stratified HR (95% CI)[b, d]	0.768 (0.339, 1.737)	
RPSFT		
N	119	60
Deaths, n (%)	29 (24.4)	17 (28.3)
Median (95% CI) (Months)[c]	NE (40.1, NE)	NE (22.8, NE)
Stratified HR (95% CI)[b, d]	0.649 (0.353, 1.192)	

CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; ITT=intent-to-treat; IWRS=interactive web response system; NE=not evaluable; NET=neuroendocrine tumor; PS=performance status; RPSFT=Rank-Preserving Structural Failure Time.

[a] Based on stratified time-dependent Cox proportional hazard regression model.

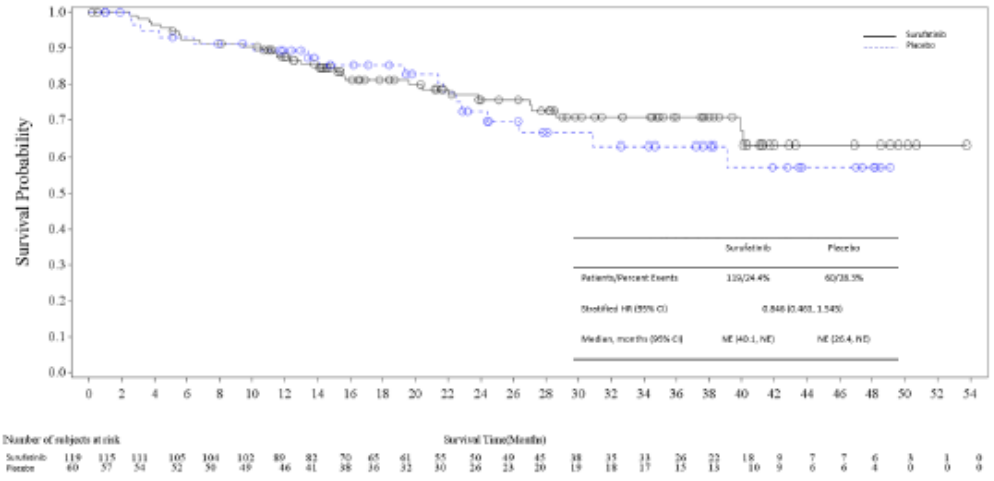
[b] The stratum was considered as 5 level as NET pathological grade=G1 regardless previous systemic antitumor drug for advanced disease and ECOG PS value, NET pathological grade=G2 by previous systemic antitumor drug for advanced disease (yes, no) and ECOG PS (0, 1) value. All factors are per IWRS. The stratum was determined at the Blinded Data Review Meeting in accordance with statistical analysis plan before interim analysis database lock.

[c] Kaplan Meier method used and 2-sided 95% CI calculated based on the Brookmeyer and Crowley method.

[d] Based on stratified Cox proportional hazard regression model.

Source: Table 14.2.2.1.2.2, Table 14.2.2.1.3.2, and Table 14.2.2.1.4.2

Figure 28. Kaplan-Meier Plot for OS (Surufatinib Versus Placebo) – ITT Set (Study 2015-012-00CH3)



CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; OS=overall survival.
Source: Figure 14.2.1.1.1.3

Table 29. Analysis of OS (surufatinib Versus Placebo; Placebo-Surufatinib Versus Placebo) – ITT Set (Study 2015-012-00CH3)

	Surufatinib (N=119)	Placebo-Surufatinib (N=43)	Placebo (N=17)
Deaths, n (%)	29 (24.4)	9 (20.9)	8 (47.1)
Median (Months)[a]	NE (40.1, NE)	NE (39.1, NE)	22.8 (3.1, NE)
Stratified HR (95% CI)[b, c] [Reference Group: placebo]	0.249 (0.109, 0.572)	0.178 (0.059, 0.535)	

CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; ITT=intent-to-treat; NE=not evaluable, OS=overall survival; PS=performance status.

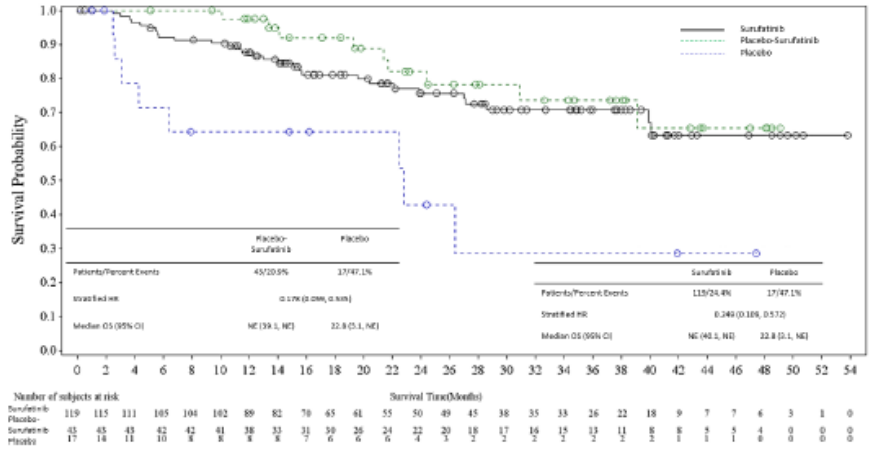
[a] Kaplan Meier method used and 2-sided 95% CI calculated based on the Brookmeyer and Crowley method.

[b] Based on stratified Cox proportional hazard regression model.

[c] Stratification factors: NET pathological grade (G1 or G2), prior use of systemic antitumor drug treatment (yes or no), and ECOG PS (0, 1). The information of stratification factors was collected based on IWRS.

Source: Table 14.2.2.1.5.2

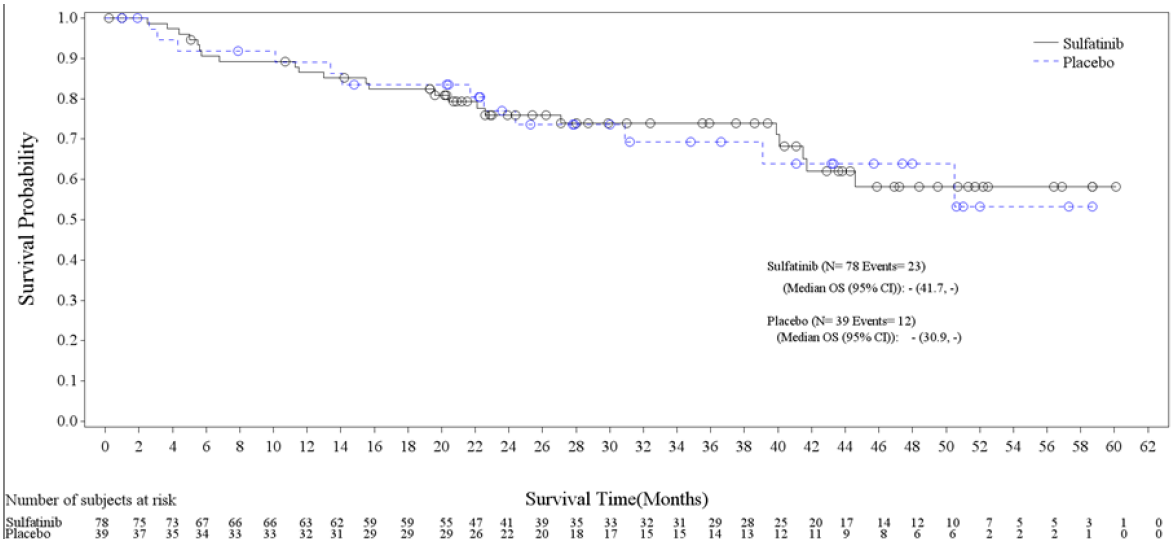
Figure 29. Kaplan-Meier Plot for OS (Surufatinib Versus Placebo) – ITT Set (Study 2015-012-00CH3)



CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; OS=overall survival.

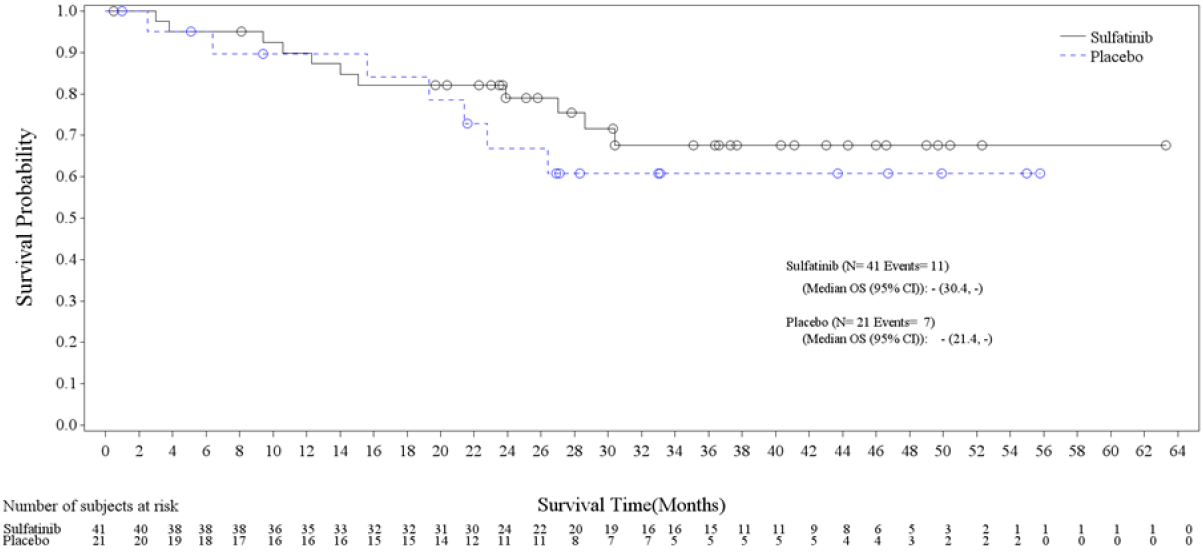
Source: Figure 14.2.1.1.1.4

Figure 30. Kaplan-Meier Curve of Overall Survival by Previous Systemic Anti-tumor Drug for Advanced Disease – Yes – ITT Set (SANET-p)



Source: Figure 14.2.1.1.4.1, Study 2015-012-00CH3

Figure 31. Kaplan-Meier Curve of Overall Survival by Previous Systemic Anti-tumor Drug for Advanced Disease – No – ITT Set (SANET-p)



Source: Figure 14.2.1.1.4.1, Study 2015-012-00CH3

Ancillary analyses

Sensitivity analyses:

Table 30. Sensitivity Analyses of Investigator-Assessed PFS (study 2015-012-00CH3)

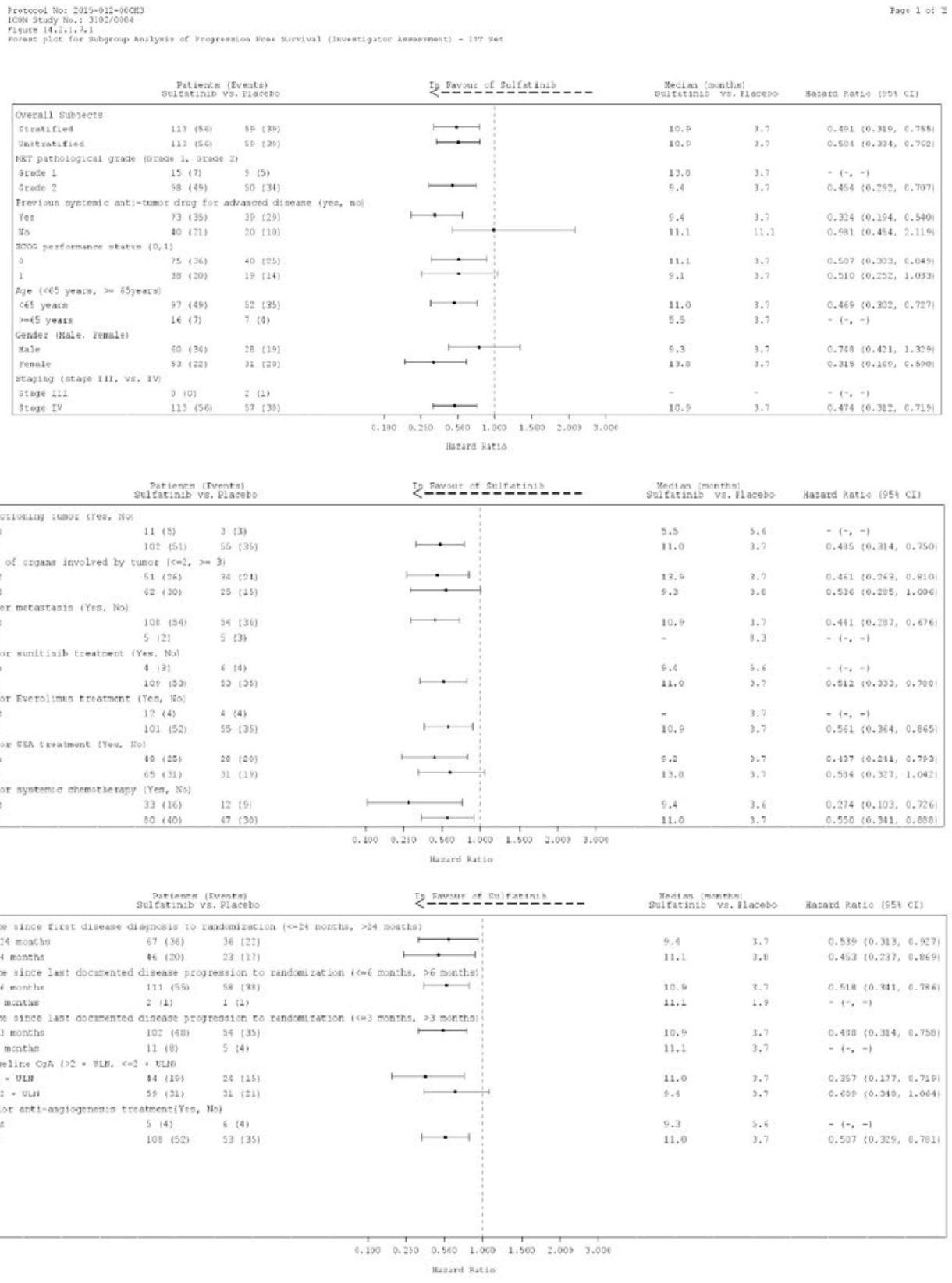
Progression-Free Survival	HR (95% CI)	p-value
Primary analysis - ITT set	0.491 (0.319, 0.755)	0.0011
Sensitivity analyses		
PP set	0.482 (0.312, 0.746)	0.0009
Treating progression/death after missed visits as progression at the next scheduled visit (ITT Set)	0.491 (0.319, 0.755)	0.0011
Using CRF stratification factors or from independent pathology review (ITT Set)	0.485 (0.315, 0.747)	0.0009
Unstratified analysis (ITT Set)	0.504 (0.334, 0.762)	0.0012
Multivariate analysis, adjusting for potential prognostic factors (exploratory analysis; ITT Set)	0.498 (0.3 , 0.8)	0.001

CRF=case report form; CSR=clinical study report; ITT=intent-to-treat; PFS=progression-free survival; PP=per protocol.

Source: Table 14.2.1.1, Table 14.2.1.2, Table 14.2.1.4, Table 14.2.1.5, Table 14.2.1.6, and Table 14.2.1.9 from the Study 2015-012-00CH3 CSR

Subgroup analyses:

Figure 32. Forest Plot of PFS Subgroup Analysis – Investigator's Evaluation – ITT Set



Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 31 Summary *of efficacy for trial 2015-012-00CH4 (SANET-ep)*

SANET-ep: A randomized, double blind, multi-center Phase III clinical study to assess the efficacy and safety of surufatinib compared to placebo in patients with advanced extrapancreatic neuroendocrine tumors.			
Study identifier	Protocol No: 2015-012-00CH4, NCT02588170		
Design	Phase III, multicentre, double-blind, randomised 2:1, placebo-controlled. After progression, unblinding was allowed and patients in the placebo arm were offered crossover to open-label surufatinib.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Not applicable, event driven Not applicable Not applicable
Hypothesis	Superiority		
Treatment groups	Surufatinib Arm		Surufatinib 300 mg once daily (QD) via oral administration (n=113 randomized); 1 treatment cycle = 4 weeks, treatment continued until disease progression, intolerable toxicity or other study criteria for termination of treatment
	Placebo Arm		Placebo QD via oral administration (n=59 randomized). 1 treatment cycle = 4 weeks, treatment continued until disease progression, intolerable toxicity or other study criteria for termination of treatment
Endpoints and definitions	Primary Endpoint	INV-PFS	Investigator-assessed progression free survival: Time from date of randomisation to date of objective disease progression or death, in accordance with RECIST version 1.1
	Secondary	INV-cORR	Investigator-assessed objective response rate: Proportion of patients that achieve confirmed complete response (CR) or partial response (PR).
	Secondary	INV-DCR	Investigator-assessed disease control rate: Proportion of patients that achieve CR, PR or stable disease (SD).
	Secondary	INV-DoR	Investigator-assessed duration of response: Duration between the date the criteria for CR or PR was first measured (first record shall prevail) and the date of disease recurrence or progression as objectively recorded
	Secondary	OS	Overall Survival: Time from date of randomisation to date of death by any cause.
Database lock	31-MAR-2019 for all analyses except OS. OS analysis based on 30-OCT-2020 data cut-off.		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT (N=198): This population includes all randomised patients and was used for the primary endpoint (INV-PFS).		
Descriptive statistics and estimate variability	Treatment group	Surufatinib Arm	Placebo Arm
	Number of subjects	129	69
	INV-PFS, patients with event (%)	77 (59.7)	51 (73.9)
	Median INV-PFS, months	9.2	3.8
	95% CI	7.4, 11.1	3.7, 5.7
	INV-cORR (%)[a]	11 (8.7)	0
	95% CI	4.4, 15.1	-
	INV-DCR (%)[a]	109 (86.5)	42 (65.6)
	95% CI	79.3, 91.9	52.7, 77.1
	INV-DoR, patients with event (%)	6 (54.5)	0
	Median DOR, months[a]	7.3	-
	95% CI	3.7, NE	-

	OS, patients with event (%)[b]	57 (39.0)		25 (34.7)
	Median OS, months	38.7		40.4
	95% CI[b]	29.7, NE		29.1, NE
Effect estimate per comparison	INV-PFS	Comparison groups	Surufatinib Arm	Placebo Arm
		Stratified HR	0.334	
		95% CI	0.223, 0.499	
		P-value	<0.0001	

Notes:
[a]iITT (interim intention to treat, n=190): This population set includes patients in the ITT set who met at least 1 of the following criteria: (1) had at least 1 post-baseline evaluable tumor assessment after the randomized treatment (at least 6 weeks from the first dose) and (2) terminated the double-blind study treatment for any reason. This population was used for the analyses dependent on response (ORR, DCR)
[b]Updated ITT (N=218): This population includes all randomised patients up to the updated analysis of OS on 30-OCT-2020

BIIRC = Blinded Independent Image Review Committee; CI = Confidence Interval; DCR – Disease Control Rate; DoR = Duration of Response; HR = Hazard Ratio; NA = Not Applicable; NE = Not Estimable; PFS = Progression Free Survival; ORR = Objective Response Rate; OS = Overall Survival

Table 32 Summary of efficacy for trial 2015-012-00CH3 (SANET-p)

SANET-p: A randomized, double blind, multi-center Phase III clinical study to assess the efficacy and safety of surufatinib compared to placebo in patients with advanced pancreatic neuroendocrine tumors.			
Study identifier	Protocol No: 2015-012-00CH3, NCT025898021		
Design	Phase III, multicentre, double-blind, randomised 2:1, placebo-controlled. After progression, unblinding was allowed and patients in the placebo arm were offered crossover to open-label surufatinib.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Not applicable, event driven Not applicable Not applicable
Hypothesis	Superiority		
Treatment groups	Surufatinib Arm		Surufatinib 300 mg once daily (QD) via oral administration (n=129 randomized); 1 treatment cycle = 4 weeks, treatment continued until disease progression, intolerable toxicity or other study criteria for termination of treatment
	Placebo Arm		Placebo QD via oral administration (n=69 randomized). 1 treatment cycle = 4 weeks, treatment continued until disease progression, intolerable toxicity or other study criteria for termination of treatment
Endpoints and definitions	Primary Endpoint	INV-PFS	Investigator-assessed progression free survival: Time from date of randomisation to date of objective disease progression or death, in accordance with RECIST version 1.1
	Secondary	INV-cORR	Investigator-assessed objective response rate: Proportion of patients that achieve confirmed complete response (CR) or partial response (PR).
	Secondary	INV-DCR	Investigator-assessed disease control rate: Proportion of patients that achieve CR, PR or stable disease (SD).
	Secondary	INV-DoR	Investigator-assessed duration of response: Duration between the date the criteria for CR or PR was first measured (first record shall prevail) and the date of disease recurrence or progression as objectively recorded
	Secondary	OS	Overall Survival: Time from date of randomisation to date of death by any cause.
Database lock	11-NOV-2019 for all analyses except OS. OS analysis based on 30-OCT-2020 data cut-off.		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT (N=172): This population includes all randomised patients and was used for the primary endpoint (INV-PFS).		
Descriptive statistics and estimate variability	Treatment group	Surufatinib Arm	Placebo Arm
	Number of subjects	113	59

	INV-PFS, patients with event (%)	56 (49.6)		39 (66.1)
	Median INV-PFS, months	10.9		3.7
	95% CI	7.5, 13.8		2.8, 5.6
	INV-cORR (%)[a]	13 (12.5)		1 (1.9)
	95% CI	6.8, 20.4		0.0, 10.1
	INV-DCR (%)[a]	84 (80.8)		35 (66.0)
	95% CI	71.9, 87.8		51.7, 78.5
	INV-DoR, patients with event (%)	6 (46.2)		0
	Median DOR, months[a]	13.3		-
	95% CI	7.0, -		-
	OS, patients with event (%)[b]	29 (24.4)		17 (28.3)
	Median OS, months	NE		NE
	95% CI[b]	40.1, NE		26.4, NE
Effect estimate per comparison	INV-PFS	Comparison groups	Surufatinib Arm	Placebo Arm
		Stratified HR	0.491	
		95% CI	0.319, 0.755	
		P-value	0.0011	

Notes:
[a]iITT (interim intention to treat, n=157): This population set includes patients in the ITT set who met at least 1 of the following criteria: (1) had at least 1 post-baseline evaluable tumor assessment after the randomized treatment (at least 6 weeks from the first dose) and (2) terminated the double-blind study treatment for any reason. This population was used for the analyses dependent on response (ORR, DCR)
[b]Updated ITT (N=179): This population includes all randomised patients up to the updated analysis of OS on 30-OCT-2020

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials 2015-012-00CH3 2015-012-00CH4	 21/172 26/198	 2/172 1/198	 0 0
Non Controlled trials 2014-012-00CH1	 13/81	 0	 0

In vitro biomarker test for patient selection for efficacy

Not applicable.

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Supportive study – 2015-012-00US1

Study 2015-012-00US1 is an ongoing, phase 1/1b, open-label, 2-part, dose escalation and dose expansion study conducted in a patient population in the US to compare the safety and efficacy results of clinical studies performed in China. The study consists of a dose escalation phase in patients with advanced solid tumors of any type and a dose expansion phase in patients with advanced cancer in 4 tumor specific cohorts: epNETs, pNETs, biliary tract cancer, and soft tissue sarcoma. The target populations in the epNET and pNET expansion cohorts are adults with low- (G1) or intermediate-grade

(G2) NETs, which are unresectable or metastatic, and who have progressed on everolimus, sunitinib, or both.

As of the data cutoff date (30 June 2020), 107 patients had been enrolled into the study (35 patients into the dose escalation phase and 72 patients into the dose expansion phase). The dose escalation phase has been completed; enrollment in the dose expansion phase is ongoing. Patients enrolled into Study 2015-012-00US1 on average were older and more racially diverse, had worse ECOG PS, and were more heavily pretreated (median prior lines of therapy: epNET, 2 [range, 1 to 8]; pNET, 4 [range, 2 to 5]).

In the dose expansion phase, the primary efficacy endpoint for the epNET and pNET cohorts was the PFS rate at 11 months. Objective response rate and DCR were secondary efficacy endpoints.

Of the 16 patients with epNETs evaluable for efficacy, 1 patient achieved a confirmed PR (ORR, 6.3%), per RECIST v1.1. Tumor growth was controlled in 15 of 16 patients (DCR, 93.8%). Of the 16 patients with pNETs evaluable for efficacy, 3 patients (18.8%) achieved a confirmed PR, and median DoR had not been reached at the time of data cutoff. Tumor growth was controlled in 14 of 16 patients (DCR, 87.5%).

The 11-month PFS rate in the epNET and pNET cohorts was 51.1% (80% CI: 24.8, 72.4) and 57.4% (80% CI: 38.9, 72.2), respectively.

To summarize, the results of Study 2015-012-00US1 confirmed the clinical dose of 300 mg QD, previously determined in studies conducted in China, in a Western patient population. Despite a heavily pretreated refractory patient population (median prior lines of therapy: epNET, 2 [range, 1 to 8]; pNET, 4 [range, 2 to 5]), the efficacy observed was consistent with the results from the SANET program and support bridging of the SANET efficacy data between regions.

In the supportive 2015-012-00US1 trial, initiated in October 2015, the population mixes patients with neuroendocrine tumours (NETs) and neuroendocrine carcinomas (NECs), noting that NEC is a separate entity, whose treatment algorithms and prognosis differ from NETs. The WHO classification from 2010 was readily available at that time, thus he justification given by the Applicant ("the term "neuroendocrine carcinoma" in prior WHO classifications –2004– was used synonymously with NET which may have been the reason for this entry into the database") is not acceptable. Remarkable uncertainty prevails over which patients were enrolled in this study and why the histologic diagnoses have been registered with contradictory terms, but the overall weight from this bridging trial remains low.

Table 33. BOR, ORR, and DCR by Disease Cohort – Efficacy Analysis Set (Study 2015-012-00US1)

	pNET (N=16)	epNET (N=16)	Total (N=32)
Confirmed BOR, n (%)			
CR	0	0	0
PR	3 (18.8)	1 (6.3)	4 (12.5)
SD	11 (68.8)	14 (87.5)	25 (78.1)
PD	1 (6.3)	1 (6.3)	2 (6.3)
NE[a]	1 (6.3)	0	1 (3.1)
ORR estimate			
Confirmed responders (CR+PR), n (%)	3 (18.8)	1 (6.3)	4 (12.5)
95% CI	(4.0, 45.6)	(0.2, 30.2)	(3.5, 29.0)

	pNET (N=16)	epNET (N=16)	Total (N=32)
DCR estimate			
Confirmed responders (CR+PR+SD), n (%)	14 (87.5)	15 (93.8)	29 (90.6)
95% CI	(61.7, 98.4)	(69.8, 99.8)	(75.0, 98.0)

BOR=best overall response; CI=confidence interval; CR=complete response; CSR=clinical study report; DCR=disease control rate; epNET=extrapancreatic neuroendocrine tumor; NE=not evaluable; ORR=objective response rate; PD=progressive disease; pNET=pancreatic neuroendocrine tumor; PR=partial response; SD=stable disease.

Note: The tumor response was determined according to the international Response Evaluation Criteria in Solid Tumors guideline Version 1.1.

Note: ORR was defined as the proportion of patients achieving a CR or PR as confirmed BOR.

Note: DCR was defined as the proportion of patients achieving a CR, PR, or SD as confirmed BOR.

Note: The denominator for the calculation of ORR and DCR was all patients in the Efficacy Analysis Set.

Note: 95% 2-sided exact CIs of ORR and DCR were based on the Clopper-Pearson method.

[a] SD too short <53 days.

Source: Table 14.2.2, Study 2015-012-00US1 CSR

Discussion on clinical efficacy

To support the marketing authorisation application (MAA) of Sevsury (surufatinib) for patients with neuroendocrine tumours (NETs), the applicant has submitted data from two pivotal phase 3 studies entirely conducted in China and supportive results from a bridging PK trial conducted in *western* patients from the USA. The updated indication at section 4.1 of the SmPC states:

> *Sevsury is indicated for use as monotherapy the treatment of adult patients with low grade (grade 1 [G1] or intermediate grade (grade 2 [G2]) progressive neuroendocrine tumours of extrapancreatic or pancreatic origin that are unresectable locally advanced or metastatic.*

Design and conduct of clinical studies

The phase 3 pivotal studies SANET-ep and SANET-p were designed and conducted synchronously, each targeting a different population (patients with extrapancreatic and pancreatic NETs, respectively), although sharing most design features, including double-blinding, 2:1 randomisation, experimental and control arms (surufatinib and placebo, respectively), primary and secondary efficacy endpoints, possibility of crossover from placebo to surufatinib at progression, and determinations on when to stop treatment – even the major protocol amendments were identical and took place at the same time. Therefore, the following discussion concerns both trials, with occasional differentiation remarks.

SANET-ep and SANET-p were conducted as of 2015 and had interim analysis with positive outcome along 2019, which according to the protocol allowed for unblinding and early termination of the studies. Scientific advice from the CHMP was sought by the applicant in April 2020, when both studies were already terminated. In their responses, the CHMP starts by asserting that since the clinical development program intended to support MAA for surufatinib seems already concluded, the potential impact of any advice is limited: the crucial idea behind requesting protocol assistance is to prospectively optimise the design of a study, in order to generate robust efficacy and safety data that would eventually allow for assessment and consideration of MAA.

Double-blind nature: Although blinding minimises the risk of biased outcomes and is thus endorsed for both trials, risk of investigator unblinding by virtue of specific surufatinib toxicity remains a drawback, especially when the comparator is placebo.

Control group: The fact that placebo was chosen as comparator arm for both trials is questionable as effective treatments for first and ulterior lines were already available and recommended by multiple international guidelines at the time of design of the studies. Grouping heterogeneous patients in the same clinical trial for whom a single common comparator cannot be identified is not an argument for using placebo as control. Separate trials could have been conducted, or investigator's choice among the approved agents used as a comparator. In the European oncology framework, placebo by itself is rarely used in trials that involve treatment-naïve patients; opposingly, it usually constitutes an 'add-on' comparator in double-blind trials. Moreover, reliable results in the meaningfully different target populations are a requirement for MAA.

Populations: The main difference between the trials, since SANET-ep recruited patients with NETs of extrapancreatic origin (e.g. small intestinal, lung, etc.), while SANET-p only permitted pancreatic NETs. The external validity of the trials and extrapolation to the European context is compromised due to:

- Use of prior treatments, including both local (e.g. liver-only disease) and systemic treatments (e.g. very low or inexistent use of sunitinib, everolimus). This hampers assessment of efficacy particularly in ≥2L patients, and we have no comprehensive data for how safe/unsafe it would be to use this drug after the patients have received standard treatments in Europe.
- Inclusion of a heterogeneous patient population, including treatment-naïve and previously treated, locally advanced unresectable and metastatic patients, and pan-anatomic primary tumours in the case of SANET-ep in a single trial, hampering the overall interpretation of efficacy results in clinically relevant sub-populations.
- Deficient baseline imaging (e.g. lack of somatostatin receptor-based scans) and unreliable recruitment requirements (lack of centralised histology review), making it difficult to fully characterize the patient population and interpret the results.
- Fundamentally different distribution of intrinsic factors (e.g. distribution of G1/G2 disease)

Hence, a corresponding target population in Europe cannot be identified. To date, none the explanations provided by the applicant solve this issue of utmost importance. The therapeutic indication is not justified by the data provided (e.g. use as line-agnostic or in locally advanced tumours or for a pan-anatomic location of primary tumours). The applicant should justify that data support the positive B/R and utility of surufatinib in EU patients irrespective of tumour characteristics and prior treatments, within the scope of the sought indication.

Regarding specific inclusion/exclusion criteria, high selectivity of patients with characteristics of better prognosis is noted, for example: functional NETs were allowed, as long as they did not require long-acting somatostating analogues to control symptoms (unlikely scenario); previous treatment with anti-VEGF/VEGFR (e.g. sunitinib) was allowed, as long as the patient did not exhibit PD while receiving it.

Cross-over to surufatinib in patients from the placebo arm who presented progressive disease was allowed as of protocol V2 in both trials, inevitably rendering any ulterior update of OS results as uninterpretable.

Endpoints: The primary endpoint of both trials was to show superior PFS from surufatinib vs. placebo: according to simultaneous BIIRC assessment in the first two versions of the protocol, and as reported by investigator since V3 (the primary analysis was in fact done upon investigator assessment of PFS events). Even if PFS is deemed an appropriate endpoint for studies on patients with advanced NETs, the major amendment that prioritised investigator assessment (instead of original BIIRC assessment) is not justified, especially when considering that relevant clinical decisions for the patients were dependent on BIIRC. In fact, 11% of subjects across both studies continued to receive the assigned treatment upon investigator's declared progression but BIIRC disagreement (non-PD), exposing their

loss of chance. Integrity of data comes also into question: the local radiologist's dictamen was not captured in the CRF and the investigators could 'change their mind' upong BIIRC's report, as it happened in several instances. Furthermore, PFS results are immature and, hence, the estimated treatment effect not reliable: early unblinding of the study with immature data and the subsequent cross over of the placebo arm patients led to a situation where no further updates on PFS would provide useful data. Moreover, the BIIRC-PFS results did not cross the efficacy boundary and the study would not have been positive at the IA. Overall, the amendment that downgrades BIIRC-PFS and prioritises INV-PFS as primary endpoint is not justified. In this context, the large discrepancy between INV and BIIRC PFS assessment is striking; not least since the directionality of this effect differs between SANET-ep and SANET-p. (SANETep: INV-PFS HR of 0.33, BIIRC-PFS HR 0.66. SANETp INV-PFS HR 0.49, BIICR-PFS HR 0.34). Although none of the explanations provided by the applicant regarding the primary endpoint drawbacks are satisfactory and there are no means to repair these decisions, the applicant should justify that the assessment of PFS in the pivotal trial is robust and fit for regulatory decision-making.

Regarding sample size calculations for both trials, the assumptions of hypothetical benefit from surufatinib as compared to placebo (HR for PFS 0.60 in SANET-ep and 0.55 in SANET-p) are indeed optimistic, an unlikely scenario had active treatment been the comparator.

Statistical methods: The dataset used for calculations of the response-dependent endpoints (ORR, DCR, DoR) excluded patients without post-baseline images or who discontinued double-blind treatment and this is not endorsed. PFS censoring rules are not completely agreed on, and additional sensitivity analyses for PFS, ORR and DCR were requested again. A considerable number of doubts arise since both studies were stopped at IA upon INV-assessed PFS results crossing the predefined efficacy boundary: OS data might have already suggested a detrimental effect in SANET-ep and there was discrepancy in INV vs. BIIRC results. Due to early stopping the results remain immature: a large number of patients had short follow-up and the studies were not fully enrolled. Because of cross-over after unblinding, concerns regarding detrimental effect on OS can no longer be reliably addressed. If a detrimental effect on OS were possibly attributable to adverse effects of surufatinib, early cross-over from the placebo arm could lead to an apparent trend towards a smaller HR. Hence, the IDMC/Sponsor decision-making process and completeness of data package provided to the IDMC remains questionable.

Patient disposition and recruitment: The overall flow of the patients is as expected, although the initial target enrolment was not reached, since both trials were terminated early. Noting a high number of patients with follow-up shorter than 3 months, significant proportion of progressors from the placebo arm of both trials were crossed over to surufatinib: 68% in SANET-ep and 76% in SANET-p. As compared to placebo, higher proportions of patients from the surufatinib arms discontinued treatment permanently because of AEs. Major protocol deviations were scant and balanced between arms of both studies. There was at least one patient who got randomised –to placebo– after the interim analysis notice, an issue that remains to be addressed by the applicant.

Baseline data: Demographic and baseline tumour characteristics between the two arms of both trials were overall balanced, noticing significantly higher proportions of G2 tumours (84% in SANET-ep and 87% in SANET-p). Questions concerning baseline/follow-up imaging and and liver-directed therapies for patients with liver disease remain to be addressed.

Efficacy data and additional analyses

SANET-ep

With 198 subjects randomised (129 surufatinib, 69 placebo) and 128 PFS events at data cut-off date (31-MAR-2019), SANET-ep met its primary endpoint: a statistically significant improvement in INV-assessed PFS was seen when comparing the surufatinib arm (mPFS 9.2 months; 95% CI 7.4, 11.1) with the placebo arm (mPFS 3.8 months; 95% CI 3.7, 5.7), for a stratified HR of 0.33 (95% CI 0.22, 0.50) and p-value <0.0001. BIIRC-assessed PFS results were similar, but showed considerably lower magnitude of benefit for the surufatinib arm: mPFS 7.4 vs. 3.9 months with placebo; HR for PFS 0.66.

OS: At the original data cut-off (31-MAR-2019), 82% of subjects were censored from OS analysis, and thus, the applicant opted not to present that preliminary analysis. An updated OS analysis with data cut-off on 30-OCT-2020 portraits 38% of OS maturity (82 deaths out of N=218) and shows mOS of 38.7 months (95% CI: 29.7, NE) in the surufatinib arm and 40.4 months (95% CI: 29.1, NE) in the placebo arm, for an estimated HR of 1.143 (95% CI 0.71, 1.85). Despite multiple justifications and post hoc analyses presented by the applicant, a detrimental effect from surufatinib upon survival has not been ruled out, hence establishing another major objection.

The clinical relevance of this seemingly positive outcome is unavoidably jeopardised. Further issues that abrogate external validity of the results include: apparent detrimental OS effect in the surufatinib arm (most likely due to toxicity), lower than expected PFS at placebo arm, overestimation of treatment effect upon early termination of the trial, inconsistent efficacy across anatomical subtypes of epNETs, impossibility to solve remaining uncertainties with updated data, low response rates in the surufatinib arm, lack of justification for the locally advanced indication, and insufficient support of IA results to perform early unblinding. None of these issues were addressed appropriately and remain unsolved.

To summarize, the results of study SANET-ep do not support a positive benefit-risk balance for surufatinib in patients with extrapancreatic neuroendocrine tumours. Regarding efficacy: PFS results are not reliable, OS is underpowered and confounded by cross-over, the number of responders is low and benefit across all anatomic locations has not been demonstrated. Of note, due to the study design, further updates on efficacy will not provide reliable information. Ultimately, given the lack of demonstrated efficacy, the safety profile is not acceptable.

SANET-p

With 172 subjects randomised (113 surufatinib, 59 placebo) and 95 PFS events at data cut-off date (11-NOV-2019), SANET-p also met its primary endpoint and declared a statistically significant improvement of INV-assessed PFS: mPFS of 10.9 months (95% CI 7.5, 13.8) in the surufatinib arm vs. 3.7 months (95% CI 2.8, 5.6) in the placebo arm, for a stratified HR of 0.49 (95% CI 0.32, 0.76) with a p-value 0.0011. BIIRC-assessed PFS results differ considerably, in this case showing a higher magnitude of benefit from surufatinib: HR 0.34.

Subgroup analysis on PFS: The PFS advantage provided by surufatinib over placebo is maintained across most of the subgroups from the population of SANET-p. However, as compared to pretreated patients, treatment-naïve patients (35% of ITT) do not show improved PFS when treated with surufatinib (mPFS 11.1) over placebo (mPFS 11.1), with a nominal HR of 0.98. This is unexpected, as most effective targeted treatments tend to show higher degree of beneficial effect in earlier lines of treatment, and furthermore, it illustrates the major difficulty in the applicability of SANET-p results into a line-agnostic context.

OS: Although still immature (26% of OS events, 46 out of N=179), the updated OS analysis, with data cut-off on 30-OCT-2020, does not indicate a potential detrimental effect of surufatinib vs. placebo: HR 0.85 (95% CI 0.46, 1.55). Median OS has nevertheless not been reached in either arm. Considering

high proportion of cross-over to surufatinib in the placebo arm (43 out of 60, 72%), an RPSFT analysis was carried out, producing comparable results.

The overall results of study SANET-p do not support positive benefit-risk balance for surufatinib in patients with pancreatic neuroendocrine tumours. Regarding efficacy: PFS are not reliable, OS is underpowered and confounded by cross-over, there is no benefit in treatment naïve-patients (contradicting general scientific knowledge, as treatment outcomes tend to improve in earlier lines), the number of responders is low, and data for ≥2L patients is too scant. Due to the study design, further updates on efficacy will not provide reliable information. Ultimately, given the lack of demonstrated efficacy, the safety profile is not acceptable.

Conclusions on clinical efficacy

Despite the seemingly positive outcome of pivotal trials SANET-ep and SANET-p, generalisability of their results to a European context is implausible. The responses provided upon major issues do not address the essential study design flaws or problems during conduct of the studies. Tremendous heterogeneity of the populations –across lines of treatment, stages and anatomic sites– does not justify lack of a single standard-of-care and thus choice of placebo as control. The amendment of primary endpoints along conduct of the trials remains unsubstantiated. Early termination of the studies upon immature PFS results and crossover of all placebo patients to surufatinib renders any updated efficacy as unreliable. Overall, efficacy of surufatinib for the intended indications is not considered established.

Moreover, late protocol amendments, discrepancies in the PFS assessment, as well as other unclarities in study conduct indicate that an inspection of GCP compliance is required prior to approval.

Clinical safety

The primary safety evaluation of surufatinib is based on data from the 2 placebo-controlled pivotal studies: SANET-ep and SANET-p (N=263, Analysis Set 1), but the summary of clinical safety (SCS) also includes data from 6 supporting open-label, monotherapy studies, as well as data from the open-label portion of the SANET-ep and SANET-p studies. The analyses were based on an integrated database that included all 8 of these monotherapy studies (N=718, Analysis Set 2). Interim analysis data cut-off date was for the 2 studies on different dates in 2019 (CSR cut-off date) and for both studies the date of study unblinding was as of 30 June 2020.

As the studies were ongoing at the data cut-off date (30 June 2020) and patients are further randomized with no planned interim analysis, study summary tables are not included in this submission. It is therefore not clear how many patients from the open-label crossover phases of the studies that are included in the data Analysis Set 2 (table 1). Also, we do not know how many of the patients in the phase 1/1b were included in Analysis Set 2 as in theory only those who received beyond 300 mg were included.

Table 34. Clinical Studies Included in the Summary of Clinical Safety

Study Phase	Study Design	Patient Population	Dosing Regimen	Study Status	No. Patients enrolled / No. Patients treated (No. Patients who received ≥300 mg surufatinib)	Data cutoff date
Clinical Studies in Patients with Cancer						
2015-012-00US1 Phase 1/1b	Phase 1b, multicenter, open-label study to evaluate safety, tolerability, and pharmacokinetics	Dose Escalation Phase: Patients with advanced solid tumors Dose Expansion Phase: Patients with advanced biliary tract cancers, patients with advanced pNETs, patients with advanced epNETs, and patients with soft tissue sarcoma	Surufatinib 50, 100, 200, 300, and 400 mg QD	Ongoing	107 / 107 (94)	30 JUN 2020
2015-012-00CH3 (SANET-p) Pivotal Phase 3	Randomized, double-blind, multicenter, placebo-controlled, phase 3 study to evaluate efficacy and safety	Patients with advanced pNETs	Surufatinib 300 mg QD; Placebo 300 mg QD	CSR completed	119 (Surufatinib 300 mg QD; 60 (Placebo 300 mg)	30 JUN 2020
	Crossover: Open-label study to evaluate safety	Patients with advanced pNETs	Surufatinib 300 mg QD	Ongoing	91	30 JUN 2020
2015-012-00CH4 (SANET-ep) Pivotal Phase 3	Randomized, double-blind, multicenter, placebo-controlled, phase 3 study to evaluate efficacy and safety	Patients with advanced epNETs	Surufatinib 300 mg QD; Placebo 300 mg QD	CSR completed	144 (Surufatinib 300 mg QD; 73 (Placebo 300 mg)	30 JUN 2020
	Crossover: Open-label study to evaluate safety	Patients with advanced epNETs	Surufatinib 300 mg QD	Ongoing	92	30 JUN 2020
2014-012-00CH1 Phase 1b/2	Phase 1b/2, open-label, multicenter study of efficacy, safety, tolerability, and pharmacokinetics	Patients with advanced NETs	Surufatinib 300 mg QD	CSR completed	81 / 81	23 AUG 2017[b]
2009-012-00CH1 Phase 1	Phase 1, open-label, multicenter, dose escalation, and dose expansion study of safety and MTD	Patients with advanced solid tumors	Surufatinib 50 to 350 mg QD	CSR completed	77 / 77 (40)	27 JUL 2012[a]

In table 1 it is seen how many patients were treated with surufatinib ≥300 mg up to the data cut-off as of 30 June 2020:

Analysis Set 1 (N=263): SANET-p: 119 patients; SANET-ep: 144 patients

Analysis Set 2 (N=718): From the phase 1 and phase 1/1b, 40 and 94 patients were included, respectively. From the open-label cross-over phases of the studies SANET-p and SANET-ep, 92 and 91 patients were included, respectively.

Patient exposure

Table 35. Summary of Exposure to Study Treatment – Analysis Set 1

	SANET-p		SANET-ep		Total	
	Surufatinib (N = 119) n (%)	Placebo (N = 60) n (%)	Surufatinib (N = 144) n (%)	Placebo (N = 73) n (%)	Surufatinib (N = 263) n (%)	Placebo (N = 133) n (%)
Duration of Exposure (Months)						
n	119	60	144	73	263	133
Mean (SD)	10.35 (8.948)	7.30 (8.614)	8.69 (7.489)	6.24 (5.473)	9.44 (8.207)	6.72 (7.055)
Median	7.6	4.4	6.9	4.8	7.4	4.6
Min, Max	0.1, 41.4	0.2, 39.9	0.2, 37.0	0.1, 30.8	0.1, 41.4	0.1, 39.9
0 - 3 Months	26 (21.8)	19 (31.7)	34 (23.6)	21 (28.8)	60 (22.8)	40 (30.1)
3 - 6 Months	25 (21.0)	23 (38.3)	26 (18.1)	22 (30.1)	51 (19.4)	45 (33.8)
6 - 9 Months	16 (13.4)	4 (6.7)	34 (23.6)	13 (17.8)	50 (19.0)	17 (12.8)
9 - 12 Months	12 (10.1)	6 (10.0)	15 (10.4)	11 (15.1)	27 (10.3)	17 (12.8)
> 12 Months	40 (33.6)	8 (13.3)	35 (24.3)	6 (8.2)	75 (28.5)	14 (10.5)
Cumulative Dose (mg)						
n	119	60	144	73	263	133
Mean (SD)	82621.0 (72029.11)	65224.2 (77681.41)	67589.9 (60016.51)	55522.6 (49470.88)	74391.1 (66021.37)	59899.2 (63683.63)
Median	57300	39300	51525	43500	54900	41400
Min, Max	900, 375900	1800, 363600	1500, 337800	900, 278700	900, 375900	900, 363600
Dose Intensity (mg/days)						
n	119	60	144	73	263	133
Mean (SD)	264.80 (39.970)	291.33 (16.395)	260.93 (40.036)	290.79 (26.128)	262.68 (39.976)	291.03 (22.194)
Median	275.5	299.6	267.7	300.0	272.6	300.0
Min, Max	128.6, 301.5	219.1, 300.0	132.8, 300.0	146.7, 301.1	128.6, 301.5	146.7, 301.1
Relative Dose Intensity (%)						
n	119	60	144	73	263	133
Mean (SD)	88.27 (13.323)	97.11 (5.464)	86.98 (13.345)	96.93 (8.709)	87.56 (13.325)	97.01 (7.398)
Median	91.8	99.9	89.2	100.0	90.9	100.0
Min, Max	42.9, 100.5	73.0, 100.0	44.3, 100.0	48.9, 100.4	42.9, 100.5	48.9, 100.4
Number of Dose Reduction						
0	63 (52.9)	53 (88.3)	71 (49.3)	64 (87.7)	134 (51.0)	117 (88.0)
1	40 (33.6)	7 (11.7)	48 (33.3)	5 (6.8)	88 (33.5)	12 (9.0)
2	14 (11.8)	0	21 (14.6)	2 (2.7)	35 (13.3)	2 (1.5)
3	2 (1.7)	0	3 (2.1)	2 (2.7)	5 (1.9)	2 (1.5)
>3	0	0	1 (0.7)	0	1 (0.4)	0
Number of Drug Interruption						
0	45 (37.8)	31 (51.7)	60 (41.7)	49 (67.1)	105 (39.9)	80 (60.2)
1	24 (20.2)	12 (20.0)	42 (29.2)	12 (16.4)	66 (25.1)	24 (18.0)
2	14 (11.8)	7 (11.7)	13 (9.0)	7 (9.6)	27 (10.3)	14 (10.5)
3	11 (9.2)	7 (11.7)	8 (5.6)	1 (1.4)	19 (7.2)	8 (6.0)
>3	25 (21.0)	3 (5.0)	21 (14.6)	4 (5.5)	46 (17.5)	7 (5.3)

Table 36. Summary of Exposure to Study Treatment – Analysis Set 2

	pNET Surufatinib (N = 229) n (%)	epNET Surufatinib (N = 265) n (%)	Surufatinib ≥300 mg Daily (N = 718) n (%)
Duration of Exposure (Months)			
n	229	265	718
Mean (SD)	12.26 (9.250)	10.25 (8.591)	8.93 (8.456)
Median	9.6	7.9	6.4
Min, Max	0.1, 46.2	0.2, 48.9	0.1, 48.9
0 - 3 Months	35 (15.3)	52 (19.6)	224 (31.2)
3 - 6 Months	36 (15.7)	41 (15.5)	113 (15.7)
6 - 9 Months	37 (16.2)	52 (19.6)	117 (16.3)
9 - 12 Months	26 (11.4)	39 (14.7)	75 (10.4)
> 12 Months	95 (41.5)	81 (30.6)	189 (26.3)
Cumulative Dose (mg)			
n	229	265	718
Mean (SD)	98499.6 (75255.70)	79686.8 (68230.52)	70818.8 (67868.13)
Median	81450	63600	50400
Min, Max	600, 419200	2100, 446700	600, 446700
Dose Intensity (mg/days)			
n	229	265	718
Mean (SD)	265.33 (38.340)	261.39 (42.065)	266.87 (42.546)
Median	279.8	270.7	284.2
Min, Max	128.6, 301.5	124.8, 342.1	124.8, 400.0
Relative Dose Intensity (%)			
n	229	265	718
Mean (SD)	88.33 (12.838)	86.77 (13.911)	88.29 (13.792)
Median	93.2	89.7	94.0
Min, Max	42.9, 100.5	41.6, 100.2	41.6, 100.5
Number of Dose Reduction			
0	118 (51.5)	134 (50.6)	410 (57.1)
1	71 (31.0)	75 (28.3)	186 (25.9)
2	31 (13.5)	45 (17.0)	99 (13.8)
3	7 (3.1)	6 (2.3)	15 (2.1)
>3	2 (0.9)	5 (1.9)	8 (1.1)

The median duration of study treatment in SANET-p/placebo and SANET-ep/placebo is 10.35/7.30 and 8.69/6.24 months, respectively. In Analysis Set 2 it was 8.93 months in the surufatinib treated patients. Patients who had ≥1 dose reduction were seen in 47.1%/11.7% and 69.4%/12.3% in SANET-p/placebo and SANET-ep/placebo, respectively. In Analysis Set 2 it happened in 42.9% of the patients. The NET-p patients were treated longer. However, they had fewer dose reductions.

Only 33.6% and 24.3% of the patients in SANET-p and SANET-ep respectively had an exposure above 12 months (Table 36 above)

Table 37. Summary of Total Exposure in Person-Years by Treatment Group – Analysis Set 1

	Surufatinib N=263		Placebo N=133	
Exposure (Months)	Patients n (%)	Person Years[a]	Patients n (%)	Person Years
0-<1	21 (8.0)	1.1	9 (6.8)	0.4
1-<3	39 (14.8)	6.7	31 (23.3)	5.5
3-<6	51 (19.4)	18.9	45 (33.8)	16.8
6-<9	48 (18.3)	29.2	17 (12.8)	9.9
9-<12	29 (11.0)	25.4	17 (12.8)	14.5
12-<15	22 (8.4)	25.0	3 (2.3)	3.5
15-<18	17 (6.5)	23.6	2 (1.5)	2.9
18-<21	11 (4.2)	17.7	3 (2.3)	4.9
21-<24	7 (2.7)	13.5	2 (1.5)	3.8
≥24	18 (6.8)	45.9	4 (3.0)	12.3

[a] Person years was calculated as number of patients x number of years exposure.
Source: Table 2.7.4.3.3.1

Table 38. Summary of Total Exposure in Person-Years by Treatment Group – Analysis Set 2

	Surufatinib N=718	
Exposure (Months)	Patients n (%)	Person Years[a]
0-<1	80 (11.1)	4.4
1-<3	144 (20.1)	23.9
3-<6	113 (15.7)	41.5
6-<9	116 (16.2)	71.1
9-<12	76 (10.6)	66.6
12-<15	43 (6.0)	48.9
15-<18	47 (6.5)	65.9
18-<21	26 (3.6)	43.1
21-<24	22 (3.1)	40.9
≥24	51 (7.1)	127.7

[a] Person years was calculated as number of patients x number of years exposure.
Source: Table 2.7.4.3.3.2

As seen in the tables 37 and 38 (analysis Set 1 and 2, respectively) about 1/4 and 1/3 of the patients already stopped treatment at 3 months in the pivotal studies and in the overall population, respectively. At 12 months 28.5% and 26.3% were still on treatment, respectively. At 15 months it was 20.2% and 20.3%, respectively. At 18 months it was 13.7% and 13.8%. At 21 months it was 9.5% and 10.2% and at 24 months only 6.8% and 7.1% were still on treatment. The exposure between the pivotal studies and the overall population was comparable.

Patient demographics and concomitant medication:

Most of the patients were enrolled in China, and in the integrated safety analysis set 2, there were 627 Asian patients, 80 non-Asian patients and 11 patients of unknown race. In China, the median age of enrolled patients was 53 years, mean body weight was 62.86 kg, and mean BMI was 22.87 kg/m2. In contrast, the median age of patients enrolled in the US was 64 years, mean body weight was 79.93 kg, and mean BMI was 27.82 kg/m2.

The applicability of Chinese data to the Western population was analyzed by the Applicant using the largest pooled surufatinib monotherapy patient population, n=718. An overview of the safety profile comparing the non-Asian and Asian patient populations is provided. According to the Applicant, these data should be interpreted with care given the small number of non-Asian patients (N=80) compared

with the much larger Asian patient pool (N=610), (+race unknown, n=28). Additionally, there is limited utility in comparing Asian and non-Asian patient populations, since the majority of the non-Asian patients were from a single open-label Phase 1 study in patients from the United States. However, the data may allow some high-level assessment of the safety profile established in the SANET-p and SANET-ep studies in comparison to the Western population.

Based on the demographics and the PopPK analysis, the Applicant states: "We can anticipate that the safety profiles will be similar between the non-Asian and Asian patient populations. Even though the non-Asian patients have a slightly higher proportion of females (increased exposure) and have higher weight and BMI (decreased exposure) compared with Asian patients, the overall effect on PopPK appears to be minimal. Even though age had no significant impact on PopPK, it is possible that there may be more AEs and greater impact seen in the older non-Asian patients compared with Asian patients." The Applicant also states that "Given that variability in weight is not spread evenly across the Asian and non-Asian populations, the differences in weight and BMI can be assessed using the overall sub-group analyses by race, and do not require separate secondary analyses by weight and BMI".

An overview of TEAEs in Asian, Non-Asian and Unknown Race including the key adverse events of special interest (AESIs) is presented in Table 39.

Table 39. Overview of TEAEs in Asian, Non-Asian and Unknown Race

Overview of TEAEs	Asian N=610 n(%)	Non-Asian N=80 n(%)	Unknown N=28 n(%)
At least 1 TEAE	601 (98.5)	76 (95.0)	27 (96.4)
TEAEs grade ≥3	439 (72.0)	57 (71.3)	19 (67.9)
Serious TEAEs	181 (29.7)	28 (35.0)	13 (46.4)
Serious TEAEs grade ≥3	140 (23.0)	24 (30.0)	10 (35.7)
TEAE - Dose Interruptions	294 (48.2)	39 (48.8)	11 (39.3)
TEAE - Dose Reductions	212 (34.8)	21 (26.3)	8 (28.6)
TEAE - Dose Interruption or Reduction	389 (63.8)	46 (57.5)	15 (53.6)
TEAE - Drug Discontinuation	107 (17.5)	12 (15.0)	8 (28.6)
TEAE - Death	24 (3.9)	4 (5.0)	1 (3.6)
AESI			
Hepatic failure, fibrosis, cirrhosis, and other liver damage related conditions (SMQ)	28 (4.6)	5 (6.3)	0
Grade ≥3	12 (2.0)	1 (1.3)	0
Proteinuria (SMQ)	477 (78.2)	19 (23.8)	18 (64.3)
Grade ≥3	94 (15.4)	7 (8.8)	3 (10.7)
Hypertension (SMQ)	382 (62.6)	31 (38.8)	13 (46.4)
Grade ≥3	186 (30.5)	21 (26.3)	6 (21.4)
Hemorrhages, excluding labs (SMQ)	213 (34.9)	13 (16.3)	11 (39.3)
Grade ≥3	25 (4.1)	2 (2.5)	5 (17.9)
Acute Renal Failure (SMQ)	27 (4.4)	1 (1.3)	1 (3.6)
Grade ≥3	6 (1.0)	0	0
Hypothyroidism (SMQ)	323 (53.0)	9 (11.3)	13 (46.4)
Grade ≥3	0	0	0

SMQ=standardised MedDRA query, TEAE=treatment emergent adverse event
Source: Table 2.7.4.4.1.2.4, Table 2.7.4.4.14.2.4

The incidence of TEAEs differ remarkably between the Asian, non-Asian and the Unknown. Serious TEAEs have very high incidence in the non-Asian (36.0%) and the Unknown (46.4%) compared to the Asian (29.7%). The concern is same for serious TEAEs ≥ grade 3, non-Asian 30.0% and Unknown 35.7% compared with the Asian 23.0%. Drug discontinuations due to TEAEs are extremely high in the Unknown, 28.6%, compared with the Asian, 17.5%, and non-Asian, 15.0%. Incidences of AESIs also

differ between races very strongly. Their incidence seems to be higher in the Asian. The Applicant justifies the differences in the incidences of TEAEs by the generally older age of patients in the non-Asian population and the generally higher age- standardized cardiovascular mortality due to ischemic heart disease, stroke and hypertension in China compared with Europe and the US (Du 2019). In addition, the Applicant emphasizes that the effect of traditional Chinese medicines (TCMs) is unknown.

Table 40. Overview of TEAEs in Asians and Non-Asians by Age Group

Overview of TEAEs	Asian <65 Years N=515 n(%)	Asian ≥65 Years N=95 n(%)	Non-Asian <65 Years N=43 n(%)	Non-Asian ≥65 Years N=37 n(%)
At least 1 TEAE	508 (98.6)	93 (97.9)	42 (97.7)	34 (91.9)
TEAEs grade ≥3	360 (69.9)	79 (83.2)	28 (65.1)	29 (78.4)
Serious TEAEs	142 (27.6)	39 (41.1)	16 (37.2)	12 (32.4)
Serious TEAEs grade ≥3	107 (20.8)	33 (34.7)	15 (34.9)	9 (24.3)
TEAE - Dose Interruptions	248 (48.2)	46 (48.4)	17 (39.5)	22 (59.5)
TEAE - Dose Reductions	172 (33.4)	40 (42.1)	7 (16.3)	14 (37.8)
TEAE - Dose Interruption or Reduction	326 (63.3)	63 (66.3)	21 (48.8)	25 (67.6)
TEAE - Drug Discontinuation	81 (15.7)	26 (27.4)	9 (20.9)	3 (8.1)
TEAE - Death	18 (3.5)	6 (6.3)	3 (7.0)	1 (2.7)
AESI				
Hepatic failure, fibrosis, cirrhosis, and other liver damage related conditions (SMQ)	22 (4.3)	6 (6.3)	3 (7.0)	2 (5.4)
Grade ≥3	10 (1.9)	2 (2.1)	1 (2.3)	0
Proteinuria (SMQ)	365 (70.9)	68 (71.6)	8 (18.6)	11 (29.7)
Grade ≥3	69 (13.4)	13 (13.7)	1 (2.3)	6 (16.2)
Hypertension (SMQ)	325 (63.1)	57 (60.0)	18 (41.9)	13 (35.1)
Grade ≥3	151 (29.3)	35 (36.8)	11 (25.6)	10 (27.0)
Hemorrhages, excluding labs (SMQ)	175 (34.0)	38 (40.0)	6 (14.0)	7 (18.9)
Grade ≥3	15 (2.9)	10 (10.5)	0	2 (5.4)
Acute Renal Failure (SMQ)	16 (3.1)	11 (11.6)	1 (2.3)	0
Grade ≥3	5 (1.0)	1 (1.1)	0	0
Hypothyroidism (SMQ)	275 (53.4)	48 (50.5)	4 (9.3)	5 (13.5)
Grade ≥3	0	0	0	0

SMQ=standardised MedDRA query, TEAE=treatment emergent adverse event
Source: Table 2.7.4.4.1.4.1.1, Table 2.7.4.4.36.1.1

The safety profile by race and age (Table 7) indicate that the higher incidence of SAEs in the non-Asian population in general is not being driven by the age since SAEs, drug discontinuations, deaths due to AEs had a lower incidence in those ≥65 years compared with those <65 years, in the non-Asian patients. This is more likely due to the underlying primary diagnoses. Similarly, age does not appear to impact the AESI profile in non-Asian patients, with some AESIs having a higher incidence in the older age group (proteinuria, hemorrhages, and hypothyroidism), and some having a lower incidence (hepatic failure, hypertension, acute renal failure).

The Applicant summarized also the safety profile by race and ECOG status. This analysis indicated that the greater proportion of ECOG status 1 versus ECOG status 0 in both Asian and non-Asian population did not have a consistent impact on the overall safety profile.

According to the Applicant, the question regarding potential differences in tumor localization is difficult to assess in the pooled surufatinib monotherapy patient population, since that data was only collected in the SANET-ep study. The demographic characteristics were generally consistent across the different tumor localizations in the SANET-ep study, although the small numbers make it challenging to draw any conclusions as to the differences.

The main conclusion can be drawn from Table 6 Overview of TEAEs in Asian, Non-Asian and Unknown Race, which strongly shows the fact that the safety profile between races vary remarkably. This reveals

the difficulty or even impossibility of conveying safety results from the Chinese population to the western population.

In summary, the applicability of Chinese data to the Western population was analyzed by the Applicant using the largest pooled surufatinib monotherapy patient population, n=718. According to the Applicant, these data should be interpreted with care given the small number of non-Asian patients compared with the much larger Asian patient pool.

The incidence of TEAEs differ remarkably between the Asian, non-Asian and the Unknown. In addition, the Applicant emphasizes that the effect of traditional Chinese medicines (TCMs) is unknown. The analysis reveals that higher incidence of SAEs in the non-Asian population is not being driven by the age. The Applicant summarized also the safety profile by race and ECOG status, which showed that the greater proportion of ECOG status 1 versus ECOG status 0 in both Asian and non-Asian population did not have a consistent impact on the overall safety profile. The question regarding potential differences in tumor localization was not possible to assess in the pooled surufatinib monotherapy patient population, since that data was only collected in the SANET-ep study.

The main conclusion can be drawn from Table 6 Overview of TEAEs in Asian, Non-Asian and Unknown Race, which strongly shows the fact that the safety profiles between races vary remarkably. This reveals the difficulty or even impossibility of conveying safety results from the Chinese population to the western population.

The most frequently administered concomitant medications were unspecified herbal and traditional medicines (53.1% of patients in safety analysis set 2).

The use of TCMs (traditional Chinese medicines) prior to the start of the SANET trials was low (<10%) for both surufatinib and placebo groups, as well as the pooled surufatinib clinical trials population.

The use of TCMs as concomitant medications during the SANET trials was higher together with surufatinib, 58.2%, than with placebo, 42.9%. The use of TCMs was similarly high in the pooled surufatinib monotherapy clinical trials at 53.1%. There were 117 TCM agents reported in the SANET trials. The lack of clarity in both the pharmaceutical ingredients, strengths and indications for these products makes it difficult to evaluate them as a class.

The impact of the use of TCM agents was analyzed mainly by comparing the profile of TEAEs before and after the start of the TCM. The overall incidence of TEAEs increased in all treatment groups after starting TCMs. Given the increase across treatment groups, this likely just reflected the increased prescription of concomitant medications as a result of TEAEs, and not a reflection of the adverse experience of TCMs per se.

The analyses of TEAEs on the placebo-treated patients provided the best opportunity to assess the safety profile of TCMs. Even though the number of patients was small, the safety profile associated with placebo-treated patients taking TCMs provided a potential surrogate since there was no confusion regarding TEAEs related to surufatinib. The profile of the TEAEs in placebo-treated patients after starting TCMs was consistent with the overall profile of the TEAEs in all placebo-treated patients.

It is currently unknown whether TCMs may have an effect on the adverse experience of surufatinib, and it is not feasible to explore this further given the multiplicity and opacity of the TCM products used both in and out of hospitals in China.

Based on the response of the Applicant, it can be summarized, that patients treated with surufatinib used more often TCMs in order to ease adverse events than patients with placebo. This fits together with the fact, that surufatinib treated patients had more adverse events than placebo treated patients in SANET trials. It remains unknown whether TCMs had an effect on the adverse experience of surufatinib, and it is not feasible to explore this further given the multiplicity and opacity of the TCM

products used both in and out of hospitals in China. However, analysis of TEAEs on the placebo-treated patients showed that the profile of the TEAEs in placebo-treated patients after starting TCMs was consistent with the overall profile of the TEAEs in all placebo-treated patients.

Adverse events

Overview of AEs:

Table 41 Overview of Treatment-Emergent Adverse Events – Analysis Set 1

	SANET-p		SANET-ep		Total	
	Surufatinib (N = 119) n (%)	Placebo (N = 60) n (%)	Surufatinib (N = 144) n (%)	Placebo (N = 73) n (%)	Surufatinib (N = 263) n (%)	Placebo (N = 133) n (%)
At Least 1 TEAE(a)	118 (99.2)	58 (96.7)	140 (97.2)	70 (95.9)	258 (98.1)	128 (96.2)
Adverse Events by CTCAE Grade(b)						
Grade 1	5 (4.2)	16 (26.7)	3 (2.1)	16 (21.9)	8 (3.0)	32 (24.1)
Grade 2	26 (21.8)	20 (33.3)	27 (18.8)	29 (39.7)	53 (20.2)	49 (36.8)
Grade 3	72 (60.5)	17 (28.3)	90 (62.5)	20 (27.4)	162 (61.6)	37 (27.8)
Grade 4	11 (9.2)	3 (5.0)	17 (11.8)	4 (5.5)	28 (10.6)	7 (5.3)
Grade 5	4 (3.4)	2 (3.3)	3 (2.1)	1 (1.4)	7 (2.7)	3 (2.3)
TEAEs Having Higher CTCAE Grade (≥3)	87 (73.1)	22 (36.7)	110 (76.4)	25 (34.2)	197 (74.9)	47 (35.3)
Serious TEAEs	33 (27.7)	10 (16.7)	37 (25.7)	14 (19.2)	70 (26.6)	24 (18.0)
Serious TEAEs of Higher CTCAE Grade (≥3)	26 (21.8)	8 (13.3)	29 (20.1)	9 (12.3)	55 (20.9)	17 (12.8)
TEAEs Leading to Drug Interruption	58 (48.7)	20 (33.3)	66 (45.8)	19 (26.0)	124 (47.1)	39 (29.3)
TEAEs Leading to Drug Reduction	48 (40.3)	3 (5.0)	65 (45.1)	6 (8.2)	113 (43.0)	9 (6.8)
TEAEs Leading to Drug Discontinuation	16 (13.4)	5 (8.3)	28 (19.4)	4 (5.5)	44 (16.7)	9 (6.8)
TEAEs Leading to Death	4 (3.4)	2 (3.3)	3 (2.1)	1 (1.4)	7 (2.7)	3 (2.3)
TEAEs of Special Interest	115 (96.6)	51 (85.0)	137 (95.1)	65 (89.0)	252 (95.8)	116 (87.2)
Drug-Related TEAEs (c)	117 (98.3)	55 (91.7)	139 (96.5)	69 (94.5)	256 (97.3)	124 (93.2)
Drug-Related TEAEs of Higher CTCAE Grade (≥3)	82 (68.9)	21 (35.0)	103 (71.5)	22 (30.1)	185 (70.3)	43 (32.3)
Drug-Related Serious TEAEs	28 (23.5)	9 (15.0)	35 (24.3)	10 (13.7)	63 (24.0)	19 (14.3)
Drug-Related Serious TEAEs of Higher CTCAE Grade (≥3)	23 (19.3)	7 (11.7)	29 (20.1)	7 (9.6)	52 (19.8)	14 (10.5)
Drug-Related TEAEs Leading to Drug Interruption	54 (45.4)	17 (28.3)	64 (44.4)	14 (19.2)	118 (44.9)	31 (23.3)
Drug-Related TEAEs Leading to Drug Reduction	48 (40.3)	3 (5.0)	65 (45.1)	5 (6.8)	113 (43.0)	8 (6.0)
Drug-Related TEAEs Leading to Drug Discontinuation	16 (13.4)	5 (8.3)	27 (18.8)	4 (5.5)	43 (16.3)	9 (6.8)
Drug-Related TEAEs Leading to Death	4 (3.4)	2 (3.3)	3 (2.1)	1 (1.4)	7 (2.7)	3 (2.3)
Drug-Related TEAEs of Special Interest	113 (95.0)	48 (80.0)	135 (93.8)	63 (86.3)	248 (94.3)	111 (83.5)

Table 42 Overview of Treatment-Emergent Adverse Events – Analysis Set 2

	pNET Surufatinib (N = 229) n (%)	epNET Surufatinib (N = 265) n (%)	Surufatinib ≥300 mg Daily (N = 718) n (%)
At Least 1 TEAE(a)	226 (98.7)	260 (98.1)	704 (98.1)
Adverse Events by CTCAE Grade(b)			
Grade 1	11 (4.8)	8 (3.0)	35 (4.9)
Grade 2	49 (21.4)	52 (19.6)	154 (21.4)
Grade 3	136 (59.4)	161 (60.8)	406 (56.5)
Grade 4	24 (10.5)	34 (12.8)	81 (11.3)
Grade 5	6 (2.6)	5 (1.9)	28 (3.9)
TEAEs Having Higher CTCAE Grade (≥3)	166 (72.5)	200 (75.5)	515 (71.7)
Serious TEAEs	65 (28.4)	83 (31.3)	222 (30.9)
Serious TEAEs of Higher CTCAE Grade (≥3)	47 (20.5)	67 (25.3)	174 (24.2)
TEAEs Leading to Drug Interruption	122 (53.3)	136 (51.3)	344 (47.9)
TEAEs Leading to Drug Reduction	79 (34.5)	108 (40.8)	241 (33.6)
TEAEs Leading to Drug Discontinuation	30 (13.1)	56 (21.1)	127 (17.7)
TEAEs Leading to Death	6 (2.6)	5 (1.9)	29 (4.0)
TEAEs of Special Interest	216 (94.3)	253 (95.5)	659 (91.8)
Drug-Related TEAEs (c)	222 (96.9)	258 (97.4)	688 (95.8)
Drug-Related TEAEs of Higher CTCAE Grade (≥3)	153 (66.8)	188 (70.9)	467 (65.0)
Drug-Related Serious TEAEs	52 (22.7)	68 (25.7)	166 (23.1)
Drug-Related Serious TEAEs of Higher CTCAE Grade (≥3)	39 (17.0)	59 (22.3)	136 (18.9)
Drug-Related TEAEs Leading to Drug Interruption	112 (48.9)	128 (48.3)	316 (44.0)
Drug-Related TEAEs Leading to Drug Reduction	79 (34.5)	107 (40.4)	238 (33.1)
Drug-Related TEAEs Leading to Drug Discontinuation	28 (12.2)	52 (19.6)	114 (15.9)
Drug-Related TEAEs Leading to Death	6 (2.6)	4 (1.5)	18 (2.5)
Drug-Related TEAEs of Special Interest	213 (93.0)	246 (92.8)	636 (88.6)

Common AEs:

Table 43. Summary of Treatment-Emergent Adverse Events with Incidence ≥10% in Total Patients Receiving Surufatinib by System Organ Class and Preferred Term – Analysis Set 1

System Organ Class Preferred Term	SANET-p		SANET-ep		Total	
	Surufatinib (N = 119) n (%)	Placebo (N = 60) n (%)	Surufatinib (N = 144) n (%)	Placebo (N = 73) n (%)	Surufatinib (N = 263) n (%)	Placebo (N = 133) n (%)
Patients with Any TEAE[a]	**118 (99.2)**	**58 (96.7)**	**140 (97.2)**	**70 (95.9)**	**258 (98.1)**	**128 (96.2)**
Investigations	108 (90.8)	54 (90.0)	127 (88.2)	57 (78.1)	235 (89.4)	111 (83.5)
Blood Thyroid Stimulating Hormone Increased	56 (47.1)	7 (11.7)	56 (38.9)	6 (8.2)	112 (42.6)	13 (9.8)
Blood Bilirubin Increased	48 (40.3)	11 (18.3)	51 (35.4)	15 (20.5)	99 (37.6)	26 (19.5)
Occult Blood Positive	36 (30.3)	15 (25.0)	51 (35.4)	14 (19.2)	87 (33.1)	29 (21.8)
Aspartate Aminotransferase Increased	32 (26.9)	23 (38.3)	49 (34.0)	18 (24.7)	81 (30.8)	41 (30.8)
Alanine Aminotransferase Increased	28 (23.5)	19 (31.7)	35 (24.3)	22 (30.1)	63 (24.0)	41 (30.8)
Weight Decreased	13 (10.9)	7 (11.7)	30 (20.8)	7 (9.6)	43 (16.3)	14 (10.5)
Blood Urine Present	19 (16.0)	6 (10.0)	23 (16.0)	7 (9.6)	42 (16.0)	13 (9.8)
Protein Urine Present	18 (15.1)	4 (6.7)	23 (16.0)	5 (6.8)	41 (15.6)	9 (6.8)
Platelet Count Decreased	19 (16.0)	0	21 (14.6)	3 (4.1)	40 (15.2)	3 (2.3)
Bilirubin Conjugated Increased	15 (12.6)	1 (1.7)	24 (16.7)	7 (9.6)	39 (14.8)	8 (6.0)
Blood Creatinine Increased	15 (12.6)	1 (1.7)	23 (16.0)	3 (4.1)	38 (14.4)	4 (3.0)
Electrocardiogram T-Wave Abnormal	12 (10.1)	5 (8.3)	20 (13.9)	4 (5.5)	32 (12.2)	9 (6.8)
Red Blood Cells Urine Positive	15 (12.6)	1 (1.7)	16 (11.1)	4 (5.5)	31 (11.8)	5 (3.8)
White Blood Cell Count Decreased	11 (9.2)	4 (6.7)	19 (13.2)	7 (9.6)	30 (11.4)	11 (8.3)
Haemoglobin Increased	13 (10.9)	0	16 (11.1)	2 (2.7)	29 (11.0)	2 (1.5)
Neutrophil Count Decreased	12 (10.1)	6 (10.0)	17 (11.8)	1 (1.4)	29 (11.0)	7 (5.3)
White Blood Cells Urine Positive	10 (8.4)	2 (3.3)	19 (13.2)	8 (11.0)	29 (11.0)	10 (7.5)
Blood Uric Acid Increased	13 (10.9)	1 (1.7)	15 (10.4)	2 (2.7)	28 (10.6)	3 (2.3)
Blood Triglycerides Increased	14 (11.8)	3 (5.0)	13 (9.0)	3 (4.1)	27 (10.3)	6 (4.5)
Renal and Urinary Disorders	85 (71.4)	35 (58.3)	106 (73.6)	39 (53.4)	191 (72.6)	74 (55.6)
Proteinuria	81 (68.1)	35 (58.3)	100 (69.4)	38 (52.1)	181 (68.8)	73 (54.9)
Gastrointestinal Disorders	83 (69.7)	36 (60.0)	107 (74.3)	39 (53.4)	190 (72.2)	75 (56.4)
Diarrhoea	61 (51.3)	16 (26.7)	68 (47.2)	14 (19.2)	129 (49.0)	30 (22.6)
Abdominal Pain	28 (23.5)	6 (10.0)	23 (16.0)	10 (13.7)	51 (19.4)	16 (12.0)
Abdominal Pain Upper	17 (14.3)	5 (8.3)	30 (20.8)	9 (12.3)	47 (17.9)	14 (10.5)
Abdominal Distension	21 (17.6)	10 (16.7)	22 (15.3)	4 (5.5)	43 (16.3)	14 (10.5)
Nausea	17 (14.3)	9 (15.0)	25 (17.4)	11 (15.1)	42 (16.0)	20 (15.0)
Vomiting	17 (14.3)	9 (15.0)	22 (15.3)	8 (11.0)	39 (14.8)	17 (12.8)
Constipation	14 (11.8)	1 (1.7)	22 (15.3)	5 (6.8)	36 (13.7)	6 (4.5)
Vascular Disorders	86 (72.3)	17 (28.3)	95 (66.0)	21 (28.8)	181 (68.8)	38 (28.6)
Hypertension	85 (71.4)	16 (26.7)	95 (66.0)	20 (27.4)	180 (68.4)	36 (27.1)
Metabolism and Nutrition Disorders	81 (68.1)	26 (43.3)	84 (58.3)	32 (43.8)	165 (62.7)	58 (43.6)
Hypertriglyceridaemia	49 (41.2)	9 (15.0)	45 (31.3)	7 (9.6)	94 (35.7)	16 (12.0)
Hypoalbuminaemia	31 (26.1)	8 (13.3)	38 (26.4)	7 (9.6)	69 (26.2)	15 (11.3)
Hyperuricaemia	28 (23.5)	2 (3.3)	26 (18.1)	5 (6.8)	54 (20.5)	7 (5.3)
Hyperglycaemia	25 (21.0)	6 (10.0)	16 (11.1)	6 (8.2)	41 (15.6)	12 (9.0)
Hypokalaemia	10 (8.4)	3 (5.0)	25 (17.4)	4 (5.5)	35 (13.3)	7 (5.3)
Decreased Appetite	13 (10.9)	6 (10.0)	18 (12.5)	8 (11.0)	31 (11.8)	14 (10.5)
Hypercholesterolaemia	15 (12.6)	4 (6.7)	16 (11.1)	4 (5.5)	31 (11.8)	8 (6.0)
Hypocalcaemia	11 (9.2)	4 (6.7)	19 (13.2)	9 (12.3)	30 (11.4)	13 (9.8)
Hypoproteinaemia	12 (10.1)	2 (3.3)	17 (11.8)	1 (1.4)	29 (11.0)	3 (2.3)

Table 44. Summary of Treatment-Emergent Adverse Events with Incidence ≥10% in Total Patients Receiving Surufatinib by System Organ Class and Preferred Term – Analysis Set 2

System Organ Class Preferred Term	pNET Surufatinib (N = 229) n (%)	epNET Surufatinib (N = 265) n (%)	Surufatinib ≥300 mg Daily (N = 718) n (%)
Patients with Any TEAE[a]	**226 (98.7)**	**260 (98.1)**	**704 (98.1)**
Investigations	199 (86.9)	241 (90.9)	594 (82.7)
Blood Bilirubin Increased	86 (37.6)	98 (37.0)	248 (34.5)
Blood Thyroid Stimulating Hormone Increased	108 (47.2)	107 (40.4)	226 (31.5)
Aspartate Aminotransferase Increased	77 (33.6)	103 (38.9)	212 (29.5)
Occult Blood Positive	67 (29.3)	94 (35.5)	181 (25.2)
Alanine Aminotransferase Increased	63 (27.5)	68 (25.7)	154 (21.4)
Platelet Count Decreased	34 (14.8)	42 (15.8)	119 (16.6)
Blood Creatinine Increased	30 (13.1)	53 (20.0)	101 (14.1)
Electrocardiogram T-Wave Abnormal	39 (17.0)	43 (16.2)	90 (12.5)
Weight Decreased	22 (9.6)	45 (17.0)	84 (11.7)
White Blood Cell Count Decreased	29 (12.7)	36 (13.6)	80 (11.1)
Bilirubin Conjugated Increased	32 (14.0)	39 (14.7)	79 (11.0)
Blood Urine Present	29 (12.7)	34 (12.8)	77 (10.7)
Blood Triglycerides Increased	33 (14.4)	38 (14.3)	75 (10.4)
Gastrointestinal Disorders	162 (70.7)	207 (78.1)	527 (73.4)
Diarrhoea	114 (49.8)	138 (52.1)	327 (45.5)
Abdominal Pain	47 (20.5)	49 (18.5)	126 (17.5)
Nausea	29 (12.7)	50 (18.9)	123 (17.1)
Vomiting	36 (15.7)	39 (14.7)	112 (15.6)
Abdominal Distension	33 (14.4)	42 (15.8)	98 (13.6)
Abdominal Pain Upper	32 (14.0)	43 (16.2)	87 (12.1)
Constipation	22 (9.6)	38 (14.3)	87 (12.1)
Renal and Urinary Disorders	172 (75.1)	203 (76.6)	495 (68.9)
Proteinuria	165 (72.1)	190 (71.7)	462 (64.3)
Haematuria	23 (10.0)	20 (7.5)	73 (10.2)
Metabolism and Nutrition Disorders	166 (72.5)	167 (63.0)	468 (65.2)
Hypertriglyceridaemia	95 (41.5)	84 (31.7)	219 (30.5)
Hypoalbuminaemia	62 (27.1)	72 (27.2)	156 (21.7)
Hyperuricaemia	56 (24.5)	61 (23.0)	153 (21.3)
Decreased Appetite	32 (14.0)	50 (18.9)	113 (15.7)
Hypoproteinaemia	26 (11.4)	47 (17.7)	109 (15.2)
Hypocalcaemia	33 (14.4)	47 (17.7)	104 (14.5)
Hypokalaemia	26 (11.4)	43 (16.2)	88 (12.3)
Hypercholesterolaemia	29 (12.7)	29 (10.9)	77 (10.7)
Hyperglycaemia	40 (17.5)	27 (10.2)	76 (10.6)

In the clinical praxis patients are treated with SSAs as backbone therapy. In this context and as already discussed in the clinical efficacy section, the use of placebo in the control arm is unacceptable for the given population. This should also be seen in the light that 1/3 of the population is treatment-naïve and furthermore, it is questioned that only very few of the enrolled population had functional status (8.1% in total, 5.1% in the placebo arm) (Table 25). This is in stark contrast to the frequencies of AEs in the placebo arm with 22.6% having diarrhoea and abdominal pain, respectively (Table 43).

Table 44. Overview of TEAE of Diarrhoea in Placebo-Treated Patients in the SANET Trials

Diarrhoea	SANET-p N=60 N (%)	SANET-ep N=73 N (%)	Total N=133 N (%)
TEAE – All grades	16 (26.7)	14 (19.2)	30 (22.6)
TEAE – grade 1 or 2	15 (25.0)	14 (19.2)	29 (21.8)
TEAE – grade 3 or 4	1 (1.7)	0	1 (0.8)
TEAE leading to dose interruption	2 (3.3)	0	2 (1.5)
TEAE leading to dose reduction	0	0	0
TEAE leading to discontinuation	0	0	0
Serious TEAE	0	0	0
TEAE leading to death	0	0	0

TEAE=treatment emergent adverse event.
Source: Table 2.7.4.4.2.1, Table 2.7.4.4.12.1, Table 2.7.4.4.11.1, Table 2.7.4.4.13.1, Table 2.7.4.4.8.1, Table 2.7.4.4.7.1

Table 45. Overview of TEAE of Abdominal Pain in Placebo-Treated Patients in the SANET Trials

Abdominal Pain	SANET-p N=60 N (%)	SANET-ep N=73 N (%)	Total N=133 N (%)
TEAE – All grades	6 (10.0)	10 (13.7)	16 (12.0)
TEAE – grade 1 or 2	6 (10.0)	9 (12.3)	15 (11.3)
TEAE – grade 3 or 4	0	1 (1.4)	1 (0.8)
TEAE leading to dose interruption	1 (1.7)	1 (1.4)	2 (1.5)
TEAE leading to dose reduction	0	0	0
TEAE leading to discontinuation	0	0	0
Serious TEAE	0	1 (1.4)	1 (0.8)
TEAE leading to death	0	0	0

TEAE=treatment emergent adverse event
Source: Table 2.7.4.4.2.1, Table 2.7.4.4.12.1, Table 2.7.4.4.11.1, Table 2.7.4.4.13.1, Table 2.7.4.4.8.1, Table 2.7.4.4.7.1

Table 46. Predisposing Risk Factors for Diarrhoea and Abdominal Pain in Placebo-Treated Patients

Placebo	Diarrhea		Abdominal pain	
	Any Grade N (%)	Grade 3 or 4 N (%)	Any Grade N (%)	Grade 3 or 4 N (%)
Functional Tumor Status				
Yes (N=5)	4 (80.0)	1 (20.0)	1 (20.0)	0
No (N=127)	26 (20.5)	0	15 (11.8)	1 (0.8)
Prior SSA Therapy				
Yes (N=47)	10 (21.3)	0	6 (12.8)	0
No (N=86)	20 (23.3)	1 (1.2)	10 (11.6)	1 (1.2)
Prior Abdominal Surgery				
Yes (N=18)	4 (22.2)	1 (5.6)	1 (5.6)	0
No (N=115)	26 (22.6)	0	15 (13.0)	1 (0.9)

SSA=somatostatin analogue
Source: Table 2.7.4.4.21.1.1, Table 2.7.4.4.21.1.2, Table 2.7.4.4.21.1.3, Table 2.7.4.4.22.1.1, Table 2.7.4.4.22.1.2, Table 2.7.4.4.22.1.3

Table 47. Use of SSAs as Concomitant Medications in the SANET Trials

Concomitant Medication by ATC2	SANET-p N=60 N (%)	SANET-ep N=73 N (%)	Total N=133 N (%)
Pituitary and hypothalamic hormones and analogues	0	4 (5.5)	4 (3.0)
Octreotide acetate	0	3 (4.1)	3 (2.3)
Octreotide	0	1 (1.4)	1 (0.8)
Somatostatin	0	1 (1.4)	1 (0.8)

ATC=anatomical therapeutic chemical, SSA=somatostatin analogue
Source: Table 2.7.4.6.1

The MAH discussed the fact that 22.5% of patients in the placebo arm experienced AEs with diarrhea and abdominal pain seen in the light that many of the patients were treatment-naïve and that concomitant SSA therapy, except for a short period only, was ruled out as an exclusion criteria. The MAH looked into the placebo-treated patients that experienced diarrhea and abdominal pain breaking down the tables according to functional status/prior SSA therapy/prior abdominal surgery. Most patients experienced Grade 1-2 AEs with only single patients experiencing Grade 3-4 AEs. According to Table 18, only 5 patients were diagnosed as having functional tumor status. However, 26 patients experienced diarrhea and 15 abdominal pain suggesting that the patients were underdiagnosed/suboptimal treated. The same is seen according to prior abdominal surgery where only 18 underwent surgery and despite of this, 30 patients experienced diarrhea and 16 abdominal pain and among these only 4 and 1 having had surgery, respectively. According to prior SSA therapy 86/133 were not previously treated and among these, 20 experienced diarrhea and 10 abdominal pain, respectively. In summary, it is not ruled out that the placebo-treated patients experienced more AEs in terms of diarrhea and abdominal pain because they obviously may have been undertreated.

The MAH discussed the AEs in the placebo-group to justify that the study was designed as a placebo-controlled study and that this fact was not detrimental to the patients. We still do not agree that there is currently no evidence-based consensus supporting SSA as first line treatment for patients having Ki-67 ≤10. Therefore, the heterogenicity of the patients enrolled in the pivotal studies do not justify the treatment strategy chosen for this subgroup of patients. This is further discussed in the assessment of the response to the major objection Question 89.

Notably 61.7% of the patients in the placebo arm had increased liver enzymes (AST or ALT), 19.5% had increased blood bilirubin and 54.9% had proteinuria which is considered unexpectedly high (Table 43)

Table 48. Overview of AST Increased TEAEs in Placebo-Treated Patients in the SANET Trials

AST Increased	SANET-p N=60 N (%)	SANET-ep N=73 N (%)	Total N=133 N (%)
TEAE – All grades	23 (38.3)	18 (24.7)	41 (30.8)
TEAE – grade 1 or 2	21 (35.0)	16 (21.9)	37 (27.8)
TEAE – grade 3 or 4	2 (3.3)	2 (2.7)	4 (3.0)
TEAE leading to dose interruption	1 (1.7)	0	1 (0.8)
TEAE leading to dose reduction	1 (1.7)	0	1 (0.8)
TEAE leading to discontinuation	0	0	0
Serious TEAE	0	0	0
TEAE leading to death	0	0	0
Liver metastases – yes	20 (33.3)	15 (20.5)	35 (26.3)
Biliary tract infection – yes	1 (1.7)	2 (2.7)	3 (2.3)
Prior gallstones / biliary surgery – yes	1 (1.7)	0	1 (0.8)

AST=aspartate aminotransferase, TEAE=treatment emergent adverse event
Source: Table 2.7.4.4.2.1, Table 2.7.4.4.12.1, Table 2.7.4.4.11.1, Table 2.7.4.4.13.1, Table 2.7.4.4.8.1, Table 2.7.4.4.7.1, Table 2.7.4.4.23.1.1, Table 2.7.4.4.23.1.2, Table 2.7.4.4.23.1.3

Table 49. Overview of ALT Increased TEAEs in Placebo-Treated Patients During the Double-Blind Treatment Phase

ALT Increased	SANET-p N=60 N (%)	SANET-ep N=73 N (%)	Total N=133 N (%)
TEAE – All grades	19 (31.7)	22 (30.1)	41 (30.8)
TEAE – grade 1 or 2	16 (26.7)	22 (30.1)	38 (28.6)
TEAE – grade 3 or 4	3 (5.0)	0	3 (2.3)
TEAE leading to dose interruption	0	0	0
TEAE leading to dose reduction	1 (1.7)	0	1 (0.8)
TEAE leading to discontinuation	0	0	0
Serious TEAE	0	0	0
TEAE leading to death	0	0	0
Liver metastases – yes	17(28.3)	20 (27.4)	37 (27.8)
Biliary tract infection – yes	1 (1.7)	2 (2.7)	3 (2.3)
Prior gallstones / biliary surgery – yes	3 (5.0)	0	3 (2.3)

ALT=alanine aminotransferase, TEAE=treatment emergent adverse event
Source: Table 2.7.4.4.2.1, Table 2.7.4.4.12.1, Table 2.7.4.4.11.1, Table 2.7.4.4.13.1, Table 2.7.4.4.8.1, Table 2.7.4.4.7.1, Table 2.7.4.4.24.1.1, Table 2.7.4.4.24.1.2, Table 2.7.4.4.24.1.3

Table. 50 Overview of Blood Bilirubin Increased TEAEs in Placebo-Treated Patients in the SANET Studies

Blood Bilirubin Increased	SANET-p N=60 N (%)	SANET-ep N=73 N (%)	Total N=133 N (%)
TEAE – All grades	11 (18.3)	15 (20.5)	26 (19.5)
TEAE – grade 1 or 2	11 (18.3)	15 (20.5)	26 (19.5)
TEAE – grade 3 or 4	0	0	0
TEAE leading to dose interruption	0	0	0
TEAE leading to dose reduction	0	0	0
TEAE leading to discontinuation	0	0	0
Serious TEAE	0	0	0
TEAE leading to death	0	0	0
Liver metastases – yes	11 (18.3)	13 (17.8)	24 (18.0)
Biliary tract infection – yes	0	1 (1.4)	1 (0.8)
Prior gallstones / biliary surgery – yes	1 (1.7)	0	1 (0.8)

TEAE=treatment emergent adverse event
Source: Table 2.7.4.4.2.1, Table 2.7.4.4.12.1, Table 2.7.4.4.11.1, Table 2.7.4.4.13.1, Table 2.7.4.4.8.1, Table 2.7.4.4.7.1, Table 2.7.4.4.25.1.1, Table 2.7.4.4.25.1.2, Table 2.7.4.4.25.1.3

Table 51. Hepatobiliary Laboratory Abnormalities in Placebo-Treated Patients in the SANET Studies in Patients with and Without Liver Metastases

Hepatobiliary Laboratory Abnormalities	SANET-p N=60 N (%)	SANET-ep N=73 N (%)	Total N=133 N (%)
Liver metastasis: Yes			
ALT or/and AST >3xULN and ≤5xULN	8 (13.3)	7 (9.6)	15 (11.3)
ALT or/and AST >5xULN	2 (3.3)	2 (2.7)	4 (3.0)
Total Bilirubin >2xULN	3 (5.0)	4 (5.5)	7 (5.3)
(ALT and/or AST >3xULN) and TB >2xULN	0	2 (2.7)	2 (1.5)
Hy's law criteria: (ALT and/or AST >3xULN) and TB >2xULN and ALP <2xULN	0	1 (1.4)	1 (0.8)
Liver metastasis: No			
ALT or/and AST >3xULN and ≤5xULN	1 (1.7)	0	1 (0.8)
ALT or/and AST >5xULN	1 (1.7)	1 (1.4)	2 (1.5)
Total Bilirubin >2xULN	0	2 (2.7)	2 (1.5)
(ALT and/or AST >3xULN) and TB >2xULN	0	1 (1.4)	1 (0.8)
Hy's law criteria: (ALT and/or AST >3xULN) and TB >2xULN and ALP <2xULN	0	1 (1.4)	1 (0.8)

ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, TB=total bilirubin, ULN=upper limit of normal
Source: Table 2.7.4.7.3.1

In the above tables the placebo-treated patients experiencing increased AST (Table 48), increased ALT (Table 49), increased bilirubin (Table 50) and hepatobiliary abnormalities breaking down the tables according to liver metastases yes/no (Table 51) can be seen. 35 and 37 out of 41 placebo-treated patients reporting AST/ALT increased, respectively had liver metastases. This explanation is as such endorsed. Regarding AST and ALT almost all were CTCAE grade 1 or 2 in severity with the exception of 4 and 3 patients experiencing a CTCAE grade 3 or 4 event, respectively. None of these patients required treatment discontinuation or dose interruption, and only 1 patient required dose reduction as a result of the event. Three patients with increased AST/ALT had biliary tract infection. One met Hy's law criteria. Of the patients not having liver metastases (Table 51) 3 had increased AST/ALT with 1 meeting Hy's law criteria. In summary, it is therefore concerning that not all patients with increased liver enzymes, having biliary tract infections or met Hy's law criteria met any treatment-related consequences. Of note, the study was double-blinded. The MAH is requested to explain the lacking dosing consequences**.** According to this and the fact that almost all patients with advanced NET have

liver metastases, the in-/exclusion criteria was inadequately described: *"Adequate hematologic and end-organ function, as defined by laboratory results".* It should have been explicitly described, and that is the normal way to do it, that when patients having liver metastases at study entry, a certain upper limit (e.g. 2.5 x ULN) should not be exceeded. It can therefore be speculated that the in-/exclusion criteria was violated. The MAH is requested to justify that this did not happen**.**

Table 52. Overview of Proteinuria TEAE in Placebo-Treated Patients in the SANET

Proteinuria	SANET-p N=60 N (%)	SANET-ep N=73 N (%)	Total N=133 N (%)
TEAE – All grades	35 (58.3)	38 (52.1)	73 (54.9)
TEAE – grade 1 or 2	34 (56.7)	38 (52.1)	72 (54.1)
TEAE – grade 3 or 4	1 (1.7)	0	1 (0.8)
TEAE leading to dose interruption	2 (3.3)	2 (2.7)	4 (3.0)
TEAE leading to dose reduction	0	1 (1.4)	1 (0.8)
TEAE leading to discontinuation	1 (1.7)	0	1 (0.8)
Serious TEAE	0	0	0
TEAE leading to death	0	0	0

Table 53. Risk factors for Proteinuria TEAE in Placebo-Treated Patients in the SANET

Placebo	Proteinuria	
	Any Grade N (%)	Grade 3 or 4 N (%)
Prior anti-VEGF Therapy		
Yes (N=8)	6 (75.0)	0
No (N=125)	67 (53.6)	1 (0.8)
Prior Chronic Kidney Disease		
Yes (N=48)	34 (70.8)	0
No (N=85)	39 (45.9)	1 (1.2)
Prior Diabetes Mellitus		
Yes (N=19)	14 (73.7)	0
No (N=114)	59 (51.8)	1 (0.9)

VEGF=vascular endothelial growth factor
Source: Table 2.7.4.4.26.1.1, Table 2.7.4.4.26.1.2, Table 2.7.4.4.26.1.3

Regarding proteinuria the MAH has provided overview tables (Tables 52 and 53). The incidence of all grade TEAE of proteinuria in the placebo-treated patients in the SANET trials was 54.9% (58.3% on SANET-p and 52.1% on SANET-ep). Almost all were CTCAE grade 1 or 2 in severity. Analysis of the predisposing risk factors for proteinuria reveals that very few placebo-treated patients had prior anti-VEGF therapy (8/133) or diabetes mellitus (19/133), and about one third had prior chronic kidney disease (48/133). Despite some of the incidences are explained by predisposing risk factors the overall incidence remains high. Other explanations could be uncontrolled hypertension or patients in a bad condition/inadequately selected for study entry.

The surufatinib treated patients had significantly more diarrhoea and abdominal pain (49% and 37.3%, respectively). The same was seen with constipation, asthenia and fatigue where it was seen in 13.7%, 16.3% and 14.1%, respectively compared to the placebo treated patients where it was seen in 4.5%, 8.3% and 4.1%, respectively (Table 43 and 44). The surufatinib treated patients seem to have a significantly worse QoL compared to patients in the placebo arm.

The following tables show the most observed AEs in the surufatinib treated patients:

Table 54. Overview of Diarrhoea TEAE for the Double-Blind SANET Trials and Pooled Surufatinib Monotherapy Studies Overall

Diarrhoea	Surufatinib 300mg N=263 N (%)	Placebo N=133 N (%)	Surufatinib Pooled N=718 N (%)
TEAE – All grades	129 (49.0)	30 (22.6)	327 (45.5)
TEAE – grade 1 or 2	123 (46.8)	29 (21.8)	303 (42.2)
TEAE – grade 3 or 4	6 (2.3)	1 (0.8)	23 (3.2)
TEAE leading to dose interruption	10 (3.8)	2 (1.5)	33 (4.6)
TEAE leading to dose reduction	3 (1.1)	0	7 (1.0)
TEAE leading to discontinuation	2 (0.8)	0	6 (0.8)
Serious TEAE	2 (0.8)	0	4 (0.6)
TEAE leading to death	0	0	1 (0.1)

TEAE=treatment emergent adverse event
Source: ISS Table 2.7.4.4.2.1, ISS Table 2.7.4.4.2.2, ISS Table 2.7.4.4.12.1, ISS Table 2.7.4.4.12.2, ISS Table 2.7.4.4.11.1, ISS Table 2.7.4.4.11.2, ISS Table 2.7.4.4.13.1, ISS Table 2.7.4.4.13.2, ISS Table 2.7.4.4.8.1, ISS Table 2.7.4.4.8.2, ISS Table 2.7.4.4.7.1, ISS Table 2.7.4.4.7.2

Diarrhea: The incidence of all grade TEAE of diarrhea was higher in the surufatinib treated patients (49.0%) versus placebo-treated patients (22.6%). Almost all were CTCAE grade 1 or 2 in severity. Given the small number of patients having any of the identified risk factors, the majority of the diarrhea events occurred in patients without the risk factors (Table 54). 2.3% had Grade 3/4. The 2 patients experiencing a SAE was deemed not related to the study drug.

Table 55. Overview of Abdominal Pain TEAE for Double-Blind SANET Trials and Pooled Surufatinib Monotherapy Studies Overall

Abdominal Pain	Surufatinib 300 mg N=263 N (%)	Placebo N=133 N (%)	Surufatinib Pooled N=718 N (%)
TEAE – All grades	51 (19.4)	16 (12.0)	126 (17.5)
TEAE – grade 1 or 2	47 (17.9)	15 (11.3)	117 (16.3)
TEAE – grade 3 or 4	4 (1.5)	1 (0.8)	9 (1.3)
TEAE leading to dose interruption	5 (1.9)	2 (1.5)	14 (1.9)
TEAE leading to dose reduction	1 (0.4)	0	1 (0.1)
TEAE leading to discontinuation	1 (0.4)	0	1 (0.1)
Serious TEAE	3 (1.1)	1 (0.8)	8 (1.1)
TEAE leading to death	0	0	0

TEAE=treatment emergent adverse event

Abdominal pain: The incidence of all grade TEAE of abdominal pain was higher in the surufatinib treated patients (19.4%) versus placebo-treated patients (12.0%). Almost all were CTCAE grade 1 or 2 in severity. 1.5% had Grade 3/4 (Table 55). The 3 patients experiencing a SAE was deemed not related to the study drug.

Table 56. Overview of Constipation TEAE in the Double-Blind SANET Trials and Pooled Monotherapy Studies Overall

Constipation	Surufatinib 300 mg N=263 N (%)	Placebo N=133 N (%)	Surufatinib Pooled N=718 N (%)
TEAE – All grades	36 (13.7)	6 (4.5)	87 (12.1)
TEAE – grade 1 or 2	36 (13.7)	6 (4.5)	86 (12.0)
TEAE – grade 3 or 4	0	0	1 (0.1)
TEAE leading to dose interruption	0	0	1 (0.1)
TEAE leading to dose reduction	0	0	0
TEAE leading to discontinuation	0	0	0
Serious TEAE	0	0	0
TEAE leading to death	0	0	0

Constipation: The incidence of all grade TEAE of constipation was higher in the surufatinib treated patients (13.7%) versus placebo-treated patients (4.5%). All were CTCAE grade 1 or 2 in severity (Table 56).

Table 57. Overview of Asthenia TEAE in Double-Blind SANET Trials and Pooled Surufatinib Monotherapy Studies Overall

Asthenia	Surufatinib 300 mg N=263 N (%)	Placebo N=133 N (%)	Surufatinib Pooled N=718 N (%)
TEAE – All grades	43 (16.3)	11 (8.3)	145 (20.2)
TEAE – grade 1 or 2	42 (16.0)	10 (7.5)	140 (19.5)
TEAE – grade 3 or 4	1 (0.4)	1 (0.8)	5 (0.7)
TEAE leading to dose interruption	1 (0.4)	1 (0.8)	6 (0.8)
TEAE leading to dose reduction	3 (1.1)	0	6 (0.8)
TEAE leading to discontinuation	1 (0.4)	0	1 (0.1)
Serious TEAE	2 (0.8)	1 (0.8)	3 (0.4)
TEAE leading to death	0	0	0

Asthenia: The incidence of all grade TEAE of asthenia was higher in the surufatinib treated patients (16.3%) versus placebo-treated patients (8.3%). Almost all were CTCAE grade 1 or 2 in severity (Table 57). There were 2 patients reporting SAEs. The investigator considered the events unlikely related to study drug.

Table 58. Overview of Fatigue TEAE for the Double-Blind SANET Trials and Pooled Surufatinib Monotherapy Studies Overall

Fatigue	Surufatinib 300 mg N=263 N (%)	Placebo N=133 N (%)	Pooled Surufatinib ≥300 mg N=718 N (%)
TEAE – All grades	37 (14.1)	6 (4.5)	79 (11.0)
TEAE – grade 1 or 2	37 (14.1)	5 (3.8)	73 (10.2)
TEAE – grade 3 or 4	0	1 (0.8)	6 (0.8)
TEAE leading to dose interruption	1 (0.4)	0	8 (1.1)
TEAE leading to dose reduction	1 (0.4)	1 (0.8)	6 (0.8)
TEAE leading to discontinuation	0	0	1 (0.1)
Serious TEAE	0	0	0
TEAE leading to death	0	0	0

Fatigue: The incidence of all grade TEAE of fatigue was higher in the surufatinib treated patients (14.1%) versus placebo-treated patients (4.5%). Almost all were CTCAE grade 1 or 2 in severity (Tabel 58).

The EORTC QoL questionnaire from both SANET-p and SANET-ep showed that the time until definitive deterioration (TUDD) was significantly shorter for diarrhea in the surufatinib treated patients versus the placebo-treated patients. Also, the difference in LS mean change from baseline for diarrhea was significantly higher (worse) in surufatinib treated patients versus placebo-treated patients. For the other conditions no significant differences were seen. In general, few patients had dose interruptions, reductions or discontinuations. Compared to the pooled population the picture was similar. In summary, the surufatinib treated patients indisputable had significantly more AEs than the placebo treated patients, and especially diarrhea is pronounced.

≥G3 AEs:

Table 59. Summary of NCI CTCAE Grade ≥3 Treatment-Emergent Adverse Events with Incidence ≥3% in Total Patients Receiving Surufatinib by System Organ Class and Preferred Term – Analysis Set 1

System Organ Class Preferred Term CTCAE Grade	SANET-p		SANET-ep		Total	
	Surufatinib (N = 119) n (%)	Placebo (N = 60) n (%)	Surufatinib (N = 144) n (%)	Placebo (N = 73) n (%)	Surufatinib (N = 263) n (%)	Placebo (N = 133) n (%)
Patients with Any CTCAE Grade ≥3 TEAE[a]	**87 (73.1)**	**22 (36.7)**	**110 (76.4)**	**25 (34.2)**	**197 (74.9)**	**47 (35.3)**
Vascular Disorders	50 (42.0)	8 (13.3)	52 (36.1)	10 (13.7)	102 (38.8)	18 (13.5)
Hypertension	50 (42.0)	8 (13.3)	52 (36.1)	10 (13.7)	102 (38.8)	18 (13.5)
Grade 3	49 (41.2)	8 (13.3)	52 (36.1)	10 (13.7)	101 (38.4)	18 (13.5)
Grade 4	1 (0.8)	0	0	0	1 (0.4)	0
Grade 5	0	0	0	0	0	0
Investigations	23 (19.3)	7 (11.7)	27 (18.8)	8 (11.0)	50 (19.0)	15 (11.3)
Aspartate Aminotransferase Increased	3 (2.5)	2 (3.3)	5 (3.5)	2 (2.7)	8 (3.0)	4 (3.0)
Grade 3	3 (2.5)	2 (3.3)	5 (3.5)	2 (2.7)	8 (3.0)	4 (3.0)
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0
Metabolism and Nutrition Disorders	21 (17.6)	0	25 (17.4)	6 (8.2)	46 (17.5)	6 (4.5)
Hypertriglyceridaemia	9 (7.6)	0	5 (3.5)	0	14 (5.3)	0
Grade 3	7 (5.9)	0	3 (2.1)	0	10 (3.8)	0
Grade 4	2 (1.7)	0	2 (1.4)	0	4 (1.5)	0
Grade 5	0	0	0	0	0	0
Hypokalaemia	3 (2.5)	0	5 (3.5)	0	8 (3.0)	0
Grade 3	2 (1.7)	0	3 (2.1)	0	5 (1.9)	0
Grade 4	1 (0.8)	0	2 (1.4)	0	3 (1.1)	0
Grade 5	0	0	0	0	0	0
Renal and Urinary Disorders	11 (9.2)	1 (1.7)	30 (20.8)	0	41 (15.6)	1 (0.8)
Proteinuria	11 (9.2)	1 (1.7)	28 (19.4)	0	39 (14.8)	1 (0.8)
Grade 3	11 (9.2)	1 (1.7)	28 (19.4)	0	39 (14.8)	1 (0.8)
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0
Blood and Lymphatic System Disorders	3 (2.5)	2 (3.3)	11 (7.6)	3 (4.1)	14 (5.3)	5 (3.8)
Anaemia	0	2 (3.3)	10 (6.9)	2 (2.7)	10 (3.8)	4 (3.0)
Grade 3	0	2 (3.3)	8 (5.6)	2 (2.7)	8 (3.0)	4 (3.0)
Grade 4	0	0	2 (1.4)	0	2 (0.8)	0
Grade 5	0	0	0	0	0	0

Table 60. Summary of NCI CTCAE Grade ≥3 Treatment-Emergent Adverse Events with Incidence ≥3% in Total Patients Receiving Surufatinib by System Organ Class and Preferred Term – Analysis Set 2

System Organ Class Preferred Term CTCAE Grade	pNET Surufatinib (N = 229) n (%)	epNET Surufatinib (N = 265) n (%)	Surufatinib ≥300 mg Daily (N = 718) n (%)
Patients with Any CTCAE Grade ≥3 TEAE[a]	**166 (72.5)**	**200 (75.5)**	**515 (71.7)**
Vascular Disorders	78 (34.1)	85 (32.1)	203 (28.3)
Hypertension	78 (34.1)	82 (30.9)	200 (27.9)
Grade 3	77 (33.6)	82 (30.9)	199 (27.7)
Grade 4	1 (0.4)	0	1 (0.1)
Grade 5	0	0	0
Investigations	43 (18.8)	50 (18.9)	140 (19.5)
Blood Bilirubin Increased	4 (1.7)	7 (2.6)	28 (3.9)
Grade 3	4 (1.7)	6 (2.3)	23 (3.2)
Grade 4	0	1 (0.4)	5 (0.7)
Grade 5	0	0	0
Metabolism and Nutrition Disorders	46 (20.1)	47 (17.7)	115 (16.0)
Hypertriglyceridaemia	20 (8.7)	8 (3.0)	32 (4.5)
Grade 3	17 (7.4)	5 (1.9)	26 (3.6)
Grade 4	3 (1.3)	3 (1.1)	6 (0.8)
Grade 5	0	0	0
Hyperuricaemia	8 (3.5)	13 (4.9)	26 (3.6)
Grade 3	0	1 (0.4)	1 (0.1)
Grade 4	8 (3.5)	12 (4.5)	25 (3.5)
Grade 5	0	0	0
Renal and Urinary Disorders	24 (10.5)	51 (19.2)	104 (14.5)
Proteinuria	23 (10.0)	43 (16.2)	89 (12.4)
Grade 3	23 (10.0)	43 (16.2)	89 (12.4)
Grade 4	0	0	0
Grade 5	0	0	0
Gastrointestinal Disorders	25 (10.9)	38 (14.3)	92 (12.8)
Diarrhoea	5 (2.2)	14 (5.3)	24 (3.3)
Grade 3	5 (2.2)	14 (5.3)	23 (3.2)
Grade 4	0	0	0
Grade 5	0	0	1 (0.1)
Blood and Lymphatic System Disorders	12 (5.2)	25 (9.4)	50 (7.0)
Anaemia	6 (2.6)	20 (7.5)	37 (5.2)
Grade 3	5 (2.2)	17 (6.4)	33 (4.6)
Grade 4	1 (0.4)	3 (1.1)	4 (0.6)
Grade 5	0	0	0

The proportion of patients with Grade ≥3 AEs in the surufatinib treated patient groups was higher than in the placebo groups (74.9% vs 35.3%) (Table 59).

The most common Grade ≥3 AEs by PT (≥3% of patients) were hypertension (38.8% vs 13.5%), proteinuria (14.8% vs 0.8%), hyperglyceridaemia (5.3% vs 0%) and anaemia (3.8% vs 3.0%) in the surufatinib treated patients compared to the placebo groups, respectively. These finding were consistent with the findings in Analysis Set 2 (Table 60).

Table 61. Overview of Hypertension TEAEs by Grade, Dose Modification, Seriousness and Time to Initiation from the Start of Study Treatment

Hypertension (SMQ Narrow Search)	Surufatinib 300 mg N=263	Placebo N=133	Surufatinib Pooled N=718
TEAE – All grades	188 (71.5%)	39 (29.3%)	426 (59.3%)
TEAE – grade 1 or 2	81 (30.8%)	20 (15.0%)	213 (29.7%)
TEAE – grade 3 or 4	107 (40.7%)	19 (14.3%)	213 (29.7%)
TEAE leading to dose interruption	20 (7.6%)	0	41 (5.7%)
TEAE leading to dose reduction	24 (9.1%)	3 (2.3%)	38 (5.3%)
TEAE leading to discontinuation	3 (1.1%)	0	8 (1.1%)
Serious TEAE	4 (1.5%)	0	7 (1.0%)
TEAE leading to death	0	0	0
TEAE Time to initiation (months) – mean (SD)	1.31 (2.79)	2.06 (3.25)	1.47 (2.97)
TEAE Time to initiation (months) – median	0.49	0.89	0.55
TEAE Time to initiation (months) – min, max	0.03, 31.18	0.03, 14.75	0.03, 31.18

Table 62. Use of Anti-Hypertensive Drugs as Concomitant Medications in Surufatinib-Treated Patients Reporting Hypertension as TEAE in ≥5 Patients

Anti-hypertensive Drugs by ATC as Concomitant Medications in Patients Reporting Hypertension as TEAE in ≥5 Patients	Surufatinib 300 mg N=188	Placebo N=39	Pooled Surufatinib ≥300 mg N=426
Any anti-hypertensive drug	111 (59.0%)	11 (28.2%)	269 (63.1%)
Time to initiation (months) – Mean (SD)	2.6 (4.76)	3.4 (7.06)	2.4 (4.15)
Time to initiation (months) – Median	1	0	1
Time to initiation (months) – Min, Max	0, 32	0, 23	0, 32
Irbesartan	35 (18.6%)	2 (5.1%)	58 (13.6%)
Valsartan	31 (16.5%)	2 (5.1%)	67 (15.7%)
Hydrochlorothiazide / Irbesartan	20 (10.6%)	1 (2.6%)	47 (11.0%)
Metoprolol tartrate	13 (6.9%)	1 (2.6%)	23 (5.4%)
Telmisar tan	11 (5.9%)	2 (5.1%)	21 (4.9%)
Captopril	9 (4.8%)	0	22 (5.2%)
Benazepril hydrochloride	8 (4.3%)	0	14 (3.3%)
Metoprolol	7 (3.7%)	0	14 (3.3%)
Losartan potassium	4 (2.1%)	0	19 (4.5%)
Hydrochlorothiazide / Valsartan	4 (2.1%)	0	10 (2.3%)
Metoprolol succinate	4 (2.1%)	0	8 (1.9%)
Candesartan cilexetil	4 (2.1%)	0	6 (1.4%)
Enalapril	3 (1.6%)	0	6 (1.4%)
Enalapril maleate	2 (1.1%)	0	14 (3.3%)
Carvedilol	2 (1.1%)	1 (2.6%)	6 (1.4%)
Amlodipine / Valsartan	2 (1.1%)	0	5 (1.2%)
Losartan	2 (1.1%)	0	5 (1.2%)
Olmesartan medoxomil	1 (0.5%)	0	10 (2.3%)
Hydrochlorothiazude / Losartan potassium	1 (0.5%)	0	7 (1.6%)
Lisinopril	0	0	16 (3.8%)
Bisoprolol fumarate	0	3 (7.7%)	5 (1.2%)
Hydralazine	0	0	5 (1.2%)

Hypertension:

The incidence of all grade TEAE of hypertension was higher in the surufatinib-treated patients (71.5%) versus placebo-treated patients (29.3%). Most were CTCAE grade 3 or 4 in severity, with 40.7% of patients on surufatinib versus 14.3% of patients on placebo (Table 61). This led to dose interruption/reduction/discontinuation in 17.9% of the surufatinib treated patients with discontinuation

seen in 1.1%. The incidence and need for dose modifications were lower in the pooled group. The time to initiation of hypertension was shorter for patients on surufatinib versus placebo (mean: 1.31 vs 2.06 months; median: 0.49 vs 0.89 month, respectively).

Among surufatinib-treated patients with hypertension, approximately 60% were prescribed at least 1 anti-hypertensive drug (Table 62). The most commonly prescribed (>10%) were valsartan, irbesartan and hydrochlorothiazide / irbesartan.

4 patients on surufatinib had hypertension as a SAE (Table 61). The MAH has provided narratives for these. They were all managed with dose interruptions and antihypertensive treatments. All 4 cases were deemed possible related to study drug. However, when looking into data on patients reporting hypertension as TEAE, there were 14 patients on surufatinib (7.4%) and 2 patients on placebo (5.1%) reporting a potential complication of hypertension. Of these, 7 surufatinib-treated patients (3.7%) reported CNS vascular disorders events, of which 5 events (Cerebral haemorrhage, Brain stem haemorrhage and Cerebrovascular accident) were serious (2.7%), 3 led to treatment discontinuation (1.6%) and 2 had a fatal outcome (1.1%). Of the remaining patients, 6 had ischaemic heart disease (3.2%) and 1 reported cardiac failure, none of which were serious or had a fatal outcome. Of the 4 cardiovascular SAEs in patients not reporting hypertension as TEAE, 2 investigators considered them to be possibly related to study drug, and 2 considered them to be not related to study drug. In all cases, there was pre-existing hypertension, left ventricular dysfunction and coronary heart disease. The MAH provided short narratives for all the events. Most of the events were deemed possible related to the study drug. According to all the narratives it is evident that all patients had a medical history of hypertension, current hypertension at the time of the event, baseline CT scans of cerebral hemorrhage or infarctions, or evidence of cerebral infarctions on CT scan at the time of the event where hypertension as AE could precipitate cerebral ischemic events, i.e. these patients may have been inadequately selected as participants in this trial. Fatal outcomes were seen for 3 of 5 of the cerebral hemorrhage patients and the brain stem hemorrhage patient. Moreover, this is also in stark contrast to the MAH's assurances of adequately treatment of hypertension with anti-hypertensives which raises serious concerns about the conduct of the trial.

Table 63. Overview of Proteinuria TEAE by Grade, Dose Modification and Time to Initiation from Start of Study Treatment

Proteinuria (SMQ Narrow Search)	Surufatinib 300mg N=263	Placebo N=133	Surufatinib Pooled N=718
TEAE – All grades	217 (82.5%)	81 (60.9%)	514 (71.6%)
TEAE – grade 1 or 2	171 (65.0%)	80 (60.2%)	410 (57.1%)
TEAE – grade 3 or 4	46 (17.5%)	1 (0.8%)	104 (14.5%)
TEAE leading to dose interruption	36 (13.7%)	5 (3.8%)	92 (12.8%)
TEAE leading to dose reduction	50 (19.0%)	1 (0.8%)	112 (15.6%)
TEAE leading to discontinuation	9 (3.4%)	1 (0.8%)	22 (3.1%)
Serious TEAE	5 (1.9%)	0	9 (1.3%)
TEAE leading to death	0	0	0
TEAE Time to initiation (months) – mean (SD)	1.76 (2.71)	2.21 (2.83)	1.96 (2.85)
TEAE Time to initiation (months) – median	0.95	0.95	0.95
TEAE Time to initiation (months) – min, max	0.16, 30.36	0.23, 16.95	0.03, 30.36

Proteinuria:

The incidence of all grade TEAE of proteinuria was higher in the surufatinib-treated patients (82.5%) versus placebo-treated patients (60.9%). As discussed earlier the latter is unexpectedly high. The incidence of all grade TEAE of proteinuria in the surufatinib-treated patients in the pooled monotherapy study population was lower than the incidence in the SANET studies (71.6% vs 82.5%) (Table 63).

Most of the TEAEs were Grade 1-2, 65.0% and 57.1%, respectively. The 5 patients on surufatinib who had proteinuria as an SAE were all deemed probably related to study drug according to the narratives. The same was seen in the 4 patients in the pooled group. The incidence of acute renal failure in the double-blind phase of the SANET trials was 1.9% in the surufatinib-treated patients compared with 0.8% in the placebo-treated patients.

Hypertension was reported as SAE in 1.5% of patients. According to the Applicant, none of these events had a fatal outcome. However, 8 patients in the analysis set 2 died due to a haemorrhage (3 cerebral, 1 brain stem, 2 gastrointestinal, 1 subdural, 1 hypovolemic shock). Many of these patients had background of uncontrolled hypertension. It can be speculated that surufatinib may have had detrimental effect on the blood pressure of these patients, which may have had impact on fatal haemorrhages.

The Applicant has explored the relationship between hypertension and the fatal cerebral and brain stem hemorrhages in detail in. In total there were 12 patients (1.7%) who experienced an SAE of CNS vascular disorders in the pooled monotherapy study Analysis Set 2 population (n=718). Narratives for these patients are presented by the Applicant. SAEs of CNS vascular disorders included 5 cerebral hemorrhages, 1 brain stem hemorrhage, 1 subdural hemorrhage, 1 cerebrovascular accident, 1 cerebellar Hemorrhage, 1 subarachnoid hemorrhage, 1 lacunar Infarction and 1 vertebrobasilar insufficiency.

Of the 12 patients who experienced an SAE of CNS vascular disorder, 6 had alternative causes for the hemorrhages:

-large hemispheric subdural hemorrhage following falls at home

-history of cerebral infarctions on baseline CT scan

-history of the presence of a space-occupying lesion in the cerebellum

-C6-T1 subarachnoid hemorrhage and cord compression secondary to pathologic fractures of the lower cervical vertebrae

-history of multiple, bilateral lacunar infarctions on MRI during the double-blind placebo phase of the study

-confirmed atherosclerosis of both common carotid arteries on ultrasound.

The remaining 6 patients (6/718, 0.8%) with an SAE of CNS vascular disorder are all possibly related to surufatinib treatment. Three of these six patients had a history of prior cerebrovascular disease (prior ischemic brain lesions at baseline, prior history of cerebral hemorrhage and lacunar infarctions and prior cerebral thrombosis). Four of the 6 patients were found to have elevated BP readings at the time of the SAE (201/101 mm Hg, 178/125 mm Hg, 163/104 mm Hg, 182/108 mm Hg). Of the 4 patients with a fatal outcome (0.6%), all had either a past history of cerebrovascular disease or cerebral infarction confirmed on CT scan.

Still, surufatinib-induced hypertension does appear to be a potential risk factor for fatal CNS vascular disorder SAEs. In spite of the guidelines concerning prevention of high blood pressure, there were 6 patients (0,8%) with an SAE of CNS vascular disorder possibly related to surufatinib treatment. Four of these six patients had highly elevated BP at the time of SAE and four of these six cases had fatal outcome. Of those four with fatal outcome, two had highly elevated BP and one did not have BP readings at the time of fatal hemorrhage. The risk of fatal CNS hemorrhages due to surufatinib-induced high blood pressure remains and will affect the assessment of benefits/risks of surufatinib.

<u>AESIs:</u>

The MAH has explained that initial AESIs were defined by a review of recognized safety issues identified from other VEGF receptor inhibitors (sunitinib, regorafenib, sorafenib, axitinib) on the market (possible class effects), and for which there was evidence from either non-clinical or phase 1 clinical studies that these would be considered important identified or important potential risks.

According to the headlines in the SCS apparently the AESIs are hypertension, haemorrhage, hepatic disorders, proteinuria, acute renal failure and thyroid disorders. The QTc prolonged has not been considered.

Table 64. Treatment Emergent Clinically Notable QT Abnormalities for Analysis Set 1 and Analysis Set 2

Criteria	Analysis Set 1		Analysis Set 2
	Surufatinib	Placebo	Surufatinib ≥300 mg Daily
	N=263	N=133	N=718
	n (%)	n (%)	n (%)
QTcF value >450 msec to ≤480 msec	24 (9.1)	6 (4.5)	71 (9.9)
QTcF value >480 msec to ≤500 msec	9 (3.4)	1 (0.8)	16 (2.2)
QTcF value >500 msec	7 (2.7)	1 (0.8)	11 (1.5)
QTcF value change from baseline >30 msec to ≤60 msec	76 (28.9)	33 (24.8)	162 (22.6)
QTcF value change of from baseline >60 msec	25 (9.5)	5 (3.8)	49 (6.8)

QTcF=QT corrected for heart rate by Fridericia's correction
Source: Table 2.7.4.9.1 & 2.7.4.9.2

Table 65. TEAEs Based on Torsades de Pointes/QT Prolongation SMQ Including Seizure

	Analysis Set 1		Analysis Set 2
	Surufatinib	Placebo	Surufatinib ≥300 mg Daily
	N=263	N=133	N=718
	n (%)	n (%)	n (%)
Subjects with TdP / QT Prolongation	6 (2.3)	2 (1.5)	17 (2.4)
Leading to Drug Reduction	0	0	0
Leading to Interruption	0	0	0
Leading to Discontinuation	0	0	2 (0.3)
Meeting SAE Criteria	0	0	1 (0.1)
Leading to Death	0	0	1 (0.1)
Grade ≥3	0	0	2 (0.3)
Electrocardiogram QT Prolonged	4 (1.5)	2 (1.5)	11 (1.5)
Loss of consciousness	2 (0.8)	0	2 (0.3)
Electrocardiogram U wave present	0	0	1 (0.1)
Multiple organ dysfunction syndrome	0	0	1 (0.1) [a]
Syncope	0	0	1 (0.1)
Ventricular arrhythmia	0	0	1 (0.1)
Seizure	0	0	1 (0.1) [b]

The non-clinical data from studies in Beagle dogs showed no significant ECG abnormalities, and the concentration-QTcF analysis on data from patients with advanced solid tumors, found no evidence of QTc prolongation at clinically relevant surufatinib concentrations.

However, there is an imbalance seen for the maximum QTcF value of >480 msec on surufatinib versus placebo (6.1% vs 1.5%) in Analysis Set 1, and the incidence is a little lower in the pooled Analysis Set 2 population for surufatinib with an incidence of 3.8%. Similarly, there is an imbalance in the QTcF change from baseline >60 msec on surufatinib versus placebo (9.5% vs 3.8%), and the incidence is again a little lower in the pooled Analysis Set 2 population for surufatinib with an incidence of 6.8% (Table 64).

TEAEs Based on Torsades de Pointes / QT Prolongation SMQ Including Seizure (Table 65) found 6 (2.3%) subjects with TdP / QT Prolongation in the surufatinib treated patients, 2 (1.5%) subjects in the placebo arm and 17 (2.4%) in the surufatinib pooled population. In the latter population 2 had treatment discontinuation, 1 had a SAE, 2 experienced Grade ≥3 and 1 died.

The MAH has provided narratives of all events and concluded that despite the imbalance seen in the proportion of patients on surufatinib compared with placebo for QTcF parameters, the majority of the patients experiencing QTcF change from baseline >60 msec had QTcF maximum values presenting borderline risk (<470 msec for females, or <450 msec for males), occurrence >3 weeks after the last dose of surufatinib, electrolyte abnormalities or took concomitant medications with known risk of QTc prolongation. The remaining 4 patients with unexplained QTcF changes did not have any clinically relevant adverse events suggesting QTc prolongation.

Nonetheless, the MAH is requested to reflect the risk of QTc prolongation in section 4.8 of the SmPC, especially the increased risk with concomitant electrolyte abnormalities or medications with known risk of QTc prolongation**.**

Table 66. Summary of AESI for Analysis Set 1 and 2 – PTs Shown for ≥2 patients in the Surufatinib 300 mg Treatment Group

	Surufatinib 300 mg (N=263)		Placebo (N=133)		Pooled Surufatinib ≥300 mg (N=718)	
AESI	Any Grade N (%)	Grade ≥3 N (%)	Any Grade N (%)	Grade ≥3 N (%)	Any Grade N (%)	Grade ≥3 N (%)
At least 1 AESI	252 (95.8)		116 (87.2)		659 (91.8)	
HEPATIC TOXICITY						
TEAE	188 (71.5)		86 (64.7)		477 (66.4)	
SAE	12 (4.6)		3 (2.3)		37 (5.2)	
Death	2 (0.8)		0		4 (0.6)	
Dose interruption	18 (6.8)		7 (5.3)		51 (7.1)	
Dose reduction	10 (3.8)		2 (1.5)		20 (2.8)	
Drug discontinuation	8 (3.0)		3 (2.3)		25 (3.5)	
Preferred Term:						
Blood bilirubin increased	99 (37.6)	5 (1.9)	26 (19.5)	0	248 (34.5)	28 (3.9)
Aspartate aminotransferase increased	81 (30.8)	8 (3.0)	41 (30.8)	4 (3.0)	212 (29.5)	21 (2.9)
Alanine aminotransferase increased	63 (24.0)	7 (2.7)	41 (30.8)	3 (2.3)	154 (21.4)	14 (1.9)
Hyperbilirubinemia	51 (19.4)	4 (1.5)	11 (8.3)	0	122 (17.0)	8 (1.1)
Bilirubin conjugated increased	39 (14.8)	1 (0.4)	8 (6.0)	0	79 (11.0)	6 (0.8)
Gamma-glutamyltransferase increased	17 (6.5)	3 (1.1)	15 (11.3)	3 (2.3)	36 (5.0)	10 (1.4)
Blood bilirubin unconjugated increased	16 (6.1)	0	6 (4.5)	0	39 (5.4)	2 (0.3)
Hepatic function abnormal	16 (6.1)	4 (1.5)	5 (3.8)	0	49 (6.8)	21 (2.9)
Urine bilirubin increased	14 (5.3)	0	2 (1.5)	0	19 (2.6)	1 (0.1)
Ascites	9 (3.4)	2 (0.8)	0	0	20 (2.8)	5 (0.7)
Hepatic pain	5 (1.9)	0	7 (5.3)	1 (0.8)	11 (1.5)	0
Total bile acids increased	4 (1.5)	1 (0.4)	2 (1.5)	0	13 (1.8)	1 (0.1)
Hepatic steatosis	3 (1.1)	0	0	0	5 (0.7)	1 (0.1)
Liver injury	3 (1.1)	3 (1.1)	0	0	6 (0.8)	4 (0.6)
Ammonia increased	2 (0.8)	0	0	0	2 (0.3)	0
Drug-induced liver injury	2 (0.8)	2 (0.8)	1 (0.8)	1 (0.8)	2 (0.3)	2 (0.3)
Hepatotoxicity	2 (0.8)	0	0	0	2 (0.3)	0
Jaundice cholestatic	2 (0.8)	2 (0.8)	3 (2.3)	3 (2.3)	10 (1.4)	10 (1.4)
HEMORRHAGES						

	Surufatinib 300 mg (N=263)		Placebo (N=133)		Pooled Surufatinib ≥300 mg (N=718)	
AESI	Any Grade N (%)	Grade ≥3 N (%)	Any Grade N (%)	Grade ≥3 N (%)	Any Grade N (%)	Grade ≥3 N (%)
TEAE	96 (36.5)		28 (21.1)		237 (33.0)	
SAE	11 (4.2)		2 (1.5)		33 (4.6)	
Death	4 (1.5)		0		8 (1.1)	
Dose interruption	11 (4.2)		3 (2.3)		27 (3.8)	
Dose reduction	4 (1.5)		1 (0.8)		10 (1.4)	
Drug discontinuation	7 (2.7)		1 (0.8)		19 (2.6)	
Preferred Term:						
Blood urine present	42 (16.0)	1 (0.4)	13 (9.8)	0	77 (10.7)	1 (0.1)
Haematuria	23 (8.7)	0	4 (3.0)	0	73 (10.2)	5 (0.7)
Gingival bleeding	19 (7.2)	0	0	0	36 (5.0)	0
Epistaxis	7 (2.7)	0	1 (0.8)	0	15 (2.1)	0
Gastrointestinal hemorrhage	6 (2.3)	4 (1.5)	2 (1.5)	0	15 (2.1)	8 (1.1)
Haematochezia	5 (1.9)	0	5 (3.8)	0	16 (2.2)	1 (0.1)
Vaginal hemorrhage	4 (1.5)	0	1 (0.8)	0	6 (0.8)	0
Cerebral hemorrhage	3 (1.1)	3 (1.1)	0	0	5 (0.7)	5 (0.7)
Haemoptysis	3 (1.1)	0	3 (2.3)	1 (0.8)	9 (1.3)	1 (0.1)
Disseminated intravascular coagulation	2 (0.8)	2 (0.8)	1 (0.8)	1 (0.8)	2 (0.3)	2 (0.3)
Menorrhagia	2 (0.8)	0	1 (0.8)	0	2 (0.3)	0
HYPERTENSION						
TEAE	188 (71.5)		39 (29.3)		426 (59.3)	
SAE	4 (1.5)		0		7 (1.0)	
Death	0		0		0	
Dose interruption	20 (7.6)		0		41 (5.7)	
Dose reduction	24 (9.1)		3 (2.3)		38 (5.3)	
Drug discontinuation	3 (1.1)		0		8 (1.1)	
Preferred Term:						
Hypertension	180 (68.4)	102 (38.8)	36 (27.1)	18 (13.5)	393 (54.7)	200 (27.9)
Blood pressure increased	12 (4.6)	6 (2.3)	4 (3.0)	1 (0.8)	42 (5.8)	14 (1.9)
PROTEINURIA						
TEAE	217 (82.5)		81 (60.9)		514 (71.6)	
SAE	5 (1.9)		0		9 (1.3)	
Death	0		0		0	
Dose interruption	36 (13.7)		5 (3.8)		92 (12.8)	
Dose reduction	50 (19.0)		1 (0.8)		112 (15.6)	
Drug discontinuation	9 (3.4)		1 (0.8)		22 (3.1)	
Preferred Term:						
Proteinuria	181 (68.8)	39 (14.8)	73 (54.9)	1 (0.8)	462 (64.3)	89 (12.4)
Protein urine present	41 (15.6)	7 (2.7)	9 (6.8)	0	66 (9.2)	14 (1.9)
Albumin urine present	4 (1.5)	0	2 (1.5)	0	8 (1.1)	0
ACUTE RENAL FAILURE						

	Surufatinib 300 mg (N=263)		Placebo (N=133)		Pooled Surufatinib ≥300 mg (N=718)	
AESI	Any Grade N (%)	Grade ≥3 N (%)	Any Grade N (%)	Grade ≥3 N (%)	Any Grade N (%)	Grade ≥3 N (%)
TEAE	5 (1.9)		1 (0.8)		29 (4.0)	
SAE	1 (0.4)		0		9 (1.3)	
Death	0		0		0	
Dose interruption	1 (0.4)		0		6 (0.8)	
Dose reduction	1 (0.4)		0		7 (1.0)	
Drug discontinuation	0		0		0	
Preferred Term:						
Oliguria	3 (1.1)	1 (0.4)	0	0	3 (0.4)	1 (0.1)
Renal impairment	2 (0.8)	0	1 (0.8)	0	6 (0.8)	0
THYROID DYSFUNCTION						
TEAE	155 (58.9)		19 (14.3)		349 (48.6)	
SAE	0		0		0	
Death	0		0		0	
Dose interruption	0		0		2 (0.3)	
Dose reduction	0		0		0	
Drug discontinuation	1 (0.4)		0		1 (0.1)	
Preferred Term:						
Blood thyroid stimulating hormone increased	112 (42.6)	0	13 (9.8)	0	226 (31.5)	0
Hypothyroidism	33 (12.5)	0	0	0	76 (10.6)	0
Tri-iodothyronine free decreased	14 (5.3)	0	3 (2.3)	0	34 (4.7)	0
Thyroxine free decreased	12 (4.6)	0	1 (0.8)	0	40 (5.6)	0
Blood thyroid stimulating hormone decreased	11 (4.2)	0	3 (2.3)	0	23 (3.2)	0
Thyroxine free increased	9 (3.4)	0	3 (2.3)	0	23 (3.2)	0
Thyroxine increased	8 (3.0)	0	1 (0.8)	0	17 (2.4)	0
Tri-iodothyronine decreased	6 (2.3)	0	3 (2.3)	0	14 (1.9)	0
Thyroid disorder	5 (1.9)	0	0	0	9 (1.3)	0
Hyperthyroidism	4 (1.5)	0	1 (0.8)	0	15 (2.1)	0
Thyroid hormones decreased	2 (0.8)	0	0	0	2 (0.3)	0
Thyroxine decreased	2 (0.8)	0	1 (0.8)	0	5 (0.7)	0
Thyroid hormones increased	2 (0.8)	0	0	0	2 (0.3)	0
Tri-iodothyronine free increased	2 (0.8)	0	3 (2.3)	0	11 (1.5)	0
Tri-iodothyronine increased	2 (0.8)	0	0	0	4 (0.6)	0

AESI=adverse event of special interest; SAE=serious adverse event; TEAE=treatment emergent adverse event
Source: Table 2.7.4.4.37.1, Table 2.7.4.4.37.2, Table 2.7.4.4.14.3.1, Table 2.7.4.4.14.3.2

Hepatic toxicity:

Any grade TEAEs was observed in 71.5% in the surufatinib arm, while it was 64.7% in the placebo arm. SAE was observed in 4.6% and 2.3%, respectively. This gave significantly more dose modifications in the surufatinib treated patients. Increased liver enzymes in the surufatinib arm were consistent with what was observed in the pooled group.

Hemorrhages:

Any grade TEAEs was observed in 36.5% in the surufatinib arm compared to 21.1% in the placebo arm. There were 4 dead in the surufatinib arm and 8 in the pooled group compared to 0 in the placebo arm. Hemorrhages were reported in 33.0% of surufatinib-treated patients across the pooled

monotherapy study population, reported as serious (4.6%) or were fatal (1.1%). The fatal events included cerebral hemorrhage (3 patients), gastrointestinal hemorrhage (2 patients), disseminated intravascular coagulation (1 patient), brain stem hemorrhage (1 patient), and subdural hemorrhage (1 patient).

Hypertension:

Any grade TEAEs was observed in 71.5% in the surufatinib arm, while it was observed in 29.3% in the placebo treated patients. SAE was seen in 1.5% in the surufatinib arm. 17.2% of the surufatinib treated patients had dose modifications with 1.1 % having dose discontinuation.

Proteinuria:

Any grade TEAEs was observed in 82.5% in the surufatinib arm, while it was observed in 60.9% in the placebo treated patients. The high proportion in the placebo arm has previously been discussed. In the surufatinb treated patients 36.1% experienced dose modifications with 1.1% having discontinuation.

Thyroid dysfunction:

Any grade TEAEs was observed in 58.9% in the surufatinib arm compared to 14.3% in the placebo arm which is a significantly difference with most patients experiencing hypothyroidism. There were no SAEs observed. Only 1 patient experienced dose discontinuation (Tabel 54).

The Applicant reports in the SCS, that "Given the potential for cerebral and gastrointestinal haemorrhages to have a fatal outcome, surufatinib treatment should be interrupted for mild to moderate haemorrhage and should be discontinued for a Grade ≥3 haemorrhagic event or where a transfusion is indicated. However, several deaths due to haemorrhages could not be prevented in surufatinib treated patients.

The deaths associated with cerebral and brain stem hemorrhage (4/8 patients) have been discussed earlier.

The other deaths associated with gastrointestinal hemorrhage and disseminated intravascular coagulation are shortly described below.

The patient with disseminated intravascular coagulation had liver metastases and had stopped study drug treatment due to anorexia requiring total parenteral nutrition, developed hepatic encephalopathy the following day and died at home a few days later.

The short narratives of the two patients with fatal gastrointestinal hemorrhage are following:

A 66-year-old male patient with a history of pNET (G2) and liver metastases developed hematemesis and bloody stool during cycle 13 of surufatinib (250 mg/day) and died at home the following day. No additional information was provided. The investigator considered the event possibly related as the patient was not taking drugs associated with bleeding, and there was no evidence of tumor invasion of the stomach or duodenum.

A 70-year-old female with gallbladder carcinoma and liver metastases developed massive hematemesis with red blood during cycle 4 of surufatinib (300 mg/day) treatment and died the same day. In the first 3 cycles, stool color was reported as yellow-brown, and routine stool and urine testing found occult blood on multiple occasions. These results were not considered to be clinically significant at the time. The investigator considered the event to be related to the study drug since the patient had no active ulcer or esophageal varices.

Given the generally higher incidence of hemorrhagic events on surufatinib compared with placebo (36.5% vs 21.1%) in Analysis Set 1, the Applicant considers that it is advisable to follow guidelines

designed to minimize the impact of hemorrhage and the SmPC (Section 4.4 Special warnings and precautions for use) includes the following:

Patients must be monitored for signs of new or worsening haemorrhagic events. Treatment for a grade 2 haemorrhagic event should be interrupted until improvement to grade 1, and the surufatinib dose reduced by 50 mg upon treatment restart. Up to 2 dose reductions may be performed. Permanent discontinuation of treatment must be made for a grade ≥3 haemorrhagic event or where a transfusion is indicated (see section 4.2).

According to the Applicant: "These guidelines emphasize the need for increased monitoring for hemorrhagic events and should enable early detection and respective intervention." But also, according to the Applicant: "The risk of fatal gastrointestinal hemorrhage may not be completely amenable to prevention given the very short event timelines in the 2 cases presented here."

The Applicant considers the currently proposed language in the SmPC as sufficient.

In summary, the Applicant has discussed, whether the intended guidelines in the SmPC are adequate for preventing fatal hemorrhages in surufatinib treated patients and considers the guidelines as sufficient. However, the evaluation of hemorrhages and the discussion of the Applicant reveals the fact that fatal gastrointestinal hemorrhages caused by surufatinib cannot be prevented by any guidelines in the SmPC given the nature of very short timelines for fatal hemorrhages. Consequently, the risk of fatal gastrointestinal hemorrhages remains, and affects the evaluation of benefit/risk -assessment of surufatinib.

Drug-related AEs:

Table 67. Summary of Drug-Related Treatment-Emergent Adverse Events with Incidence ≥10% in Total Patients Receiving Surufatinib by System Organ Class and Preferred Term – Analysis Set 1

System Organ Class Preferred Term	SANET-p		SANET-ep		Total	
	Surufatinib (N = 119) n (%)	Placebo (N = 60) n (%)	Surufatinib (N = 144) n (%)	Placebo (N = 73) n (%)	Surufatinib (N = 263) n (%)	Placebo (N = 133) n (%)
Patients with Any Drug-Related TEAE[a]	**117 (98.3)**	**55 (91.7)**	**139 (96.5)**	**69 (94.5)**	**256 (97.3)**	**124 (93.2)**
Investigations	106 (89.1)	52 (86.7)	126 (87.5)	57 (78.1)	232 (88.2)	109 (82.0)
Blood Thyroid Stimulating Hormone Increased	54 (45.4)	7 (11.7)	55 (38.2)	6 (8.2)	109 (41.4)	13 (9.8)
Blood Bilirubin Increased	48 (40.3)	11 (18.3)	50 (34.7)	15 (20.5)	98 (37.3)	26 (19.5)
Aspartate Aminotransferase Increased	32 (26.9)	22 (36.7)	49 (34.0)	18 (24.7)	81 (30.8)	40 (30.1)
Occult Blood Positive	33 (27.7)	14 (23.3)	47 (32.6)	14 (19.2)	80 (30.4)	28 (21.1)
Alanine Aminotransferase Increased	26 (21.8)	18 (30.0)	34 (23.6)	22 (30.1)	60 (22.8)	40 (30.1)
Protein Urine Present	18 (15.1)	4 (6.7)	23 (16.0)	4 (5.5)	41 (15.6)	8 (6.0)
Blood Urine Present	18 (15.1)	5 (8.3)	22 (15.3)	7 (9.6)	40 (15.2)	12 (9.0)
Platelet Count Decreased	19 (16.0)	0	21 (14.6)	3 (4.1)	40 (15.2)	3 (2.3)
Bilirubin Conjugated Increased	15 (12.6)	1 (1.7)	24 (16.7)	7 (9.6)	39 (14.8)	8 (6.0)
Weight Decreased	12 (10.1)	6 (10.0)	27 (18.8)	5 (6.8)	39 (14.8)	11 (8.3)
Blood Creatinine Increased	15 (12.6)	1 (1.7)	23 (16.0)	2 (2.7)	38 (14.4)	3 (2.3)
Electrocardiogram T-Wave Abnormal	10 (8.4)	5 (8.3)	19 (13.2)	4 (5.5)	29 (11.0)	9 (6.8)
Haemoglobin Increased	13 (10.9)	0	16 (11.1)	2 (2.7)	29 (11.0)	2 (1.5)
Neutrophil Count Decreased	12 (10.1)	6 (10.0)	17 (11.8)	1 (1.4)	29 (11.0)	7 (5.3)
White Blood Cell Count Decreased	11 (9.2)	4 (6.7)	18 (12.5)	6 (8.2)	29 (11.0)	10 (7.5)
Blood Uric Acid Increased	13 (10.9)	1 (1.7)	15 (10.4)	2 (2.7)	28 (10.6)	3 (2.3)
Blood Triglycerides Increased	14 (11.8)	3 (5.0)	13 (9.0)	3 (4.1)	27 (10.3)	6 (4.5)
Red Blood Cells Urine Positive	14 (11.8)	0	13 (9.0)	4 (5.5)	27 (10.3)	4 (3.0)
Gastrointestinal Disorders	81 (68.1)	32 (53.3)	106 (73.6)	34 (46.6)	187 (71.1)	66 (49.6)
Diarrhoea	61 (51.3)	16 (26.7)	66 (45.8)	12 (16.4)	127 (48.3)	28 (21.1)
Abdominal Pain	26 (21.8)	6 (10.0)	22 (15.3)	5 (6.8)	48 (18.3)	11 (8.3)
Abdominal Distension	21 (17.6)	9 (15.0)	20 (13.9)	4 (5.5)	41 (15.6)	13 (9.8)
Abdominal Pain Upper	15 (12.6)	4 (6.7)	26 (18.1)	8 (11.0)	41 (15.6)	12 (9.0)
Nausea	17 (14.3)	9 (15.0)	24 (16.7)	9 (12.3)	41 (15.6)	18 (13.5)
Vomiting	16 (13.4)	9 (15.0)	21 (14.6)	5 (6.8)	37 (14.1)	14 (10.5)
Constipation	11 (9.2)	0	17 (11.8)	4 (5.5)	28 (10.6)	4 (3.0)
Renal and Urinary Disorders	82 (68.9)	31 (51.7)	100 (69.4)	35 (47.9)	182 (69.2)	66 (49.6)
Proteinuria	80 (67.2)	31 (51.7)	95 (66.0)	34 (46.6)	175 (66.5)	65 (48.9)
Vascular Disorders	84 (70.6)	15 (25.0)	95 (66.0)	21 (28.8)	179 (68.1)	36 (27.1)
Hypertension	83 (69.7)	14 (23.3)	95 (66.0)	20 (27.4)	178 (67.7)	34 (25.6)
Metabolism and Nutrition Disorders	76 (63.9)	23 (38.3)	79 (54.9)	27 (37.0)	155 (58.9)	50 (37.6)
Hypertriglyceridaemia	49 (41.2)	5 (8.3)	42 (29.2)	6 (8.2)	91 (34.6)	11 (8.3)
Hyperuricaemia	25 (21.0)	2 (3.3)	23 (16.0)	4 (5.5)	48 (18.3)	6 (4.5)
Hypoalbuminaemia	21 (17.6)	7 (11.7)	25 (17.4)	4 (5.5)	46 (17.5)	11 (8.3)
Decreased Appetite	13 (10.9)	5 (8.3)	16 (11.1)	6 (8.2)	29 (11.0)	11 (8.3)
Hyperglycaemia	19 (16.0)	5 (8.3)	10 (6.9)	4 (5.5)	29 (11.0)	9 (6.8)
Hypercholesterolaemia	15 (12.6)	3 (5.0)	13 (9.0)	3 (4.1)	28 (10.6)	6 (4.5)

Table 68. Summary of Drug-Related Treatment-Emergent Adverse Events with Incidence ≥10% in Total Patients Receiving Surufatinib by System Organ Class and Preferred Term – Analysis Set 2

System Organ Class Preferred Term	pNET Surufatinib (N = 229) n (%)	epNET Surufatinib (N = 265) n (%)	Surufatinib ≥300 mg Daily (N = 718) n (%)
Patients with Any Drug-Related TEAE[a]	**222 (96.9)**	**258 (97.4)**	**688 (95.8)**
Investigations	194 (84.7)	234 (88.3)	568 (79.1)
Blood Bilirubin Increased	83 (36.2)	96 (36.2)	235 (32.7)
Blood Thyroid Stimulating Hormone Increased	104 (45.4)	106 (40.0)	220 (30.6)
Aspartate Aminotransferase Increased	73 (31.9)	101 (38.1)	202 (28.1)
Occult Blood Positive	60 (26.2)	84 (31.7)	163 (22.7)
Alanine Aminotransferase Increased	58 (25.3)	65 (24.5)	143 (19.9)
Platelet Count Decreased	32 (14.0)	42 (15.8)	115 (16.0)
Blood Creatinine Increased	27 (11.8)	50 (18.9)	91 (12.7)
Electrocardiogram T-Wave Abnormal	35 (15.3)	39 (14.7)	82 (11.4)
White Blood Cell Count Decreased	29 (12.7)	35 (13.2)	79 (11.0)
Bilirubin Conjugated Increased	31 (13.5)	38 (14.3)	77 (10.7)
Blood Triglycerides Increased	32 (14.0)	38 (14.3)	74 (10.3)
Blood Urine Present	27 (11.8)	32 (12.1)	72 (10.0)
Gastrointestinal Disorders	153 (66.8)	200 (75.5)	487 (67.8)
Diarrhoea	111 (48.5)	134 (50.6)	312 (43.5)
Nausea	28 (12.2)	45 (17.0)	108 (15.0)
Abdominal Pain	39 (17.0)	41 (15.5)	100 (13.9)
Vomiting	32 (14.0)	35 (13.2)	95 (13.2)
Abdominal Distension	28 (12.2)	37 (14.0)	80 (11.1)
Renal and Urinary Disorders	163 (71.2)	188 (70.9)	463 (64.5)
Proteinuria	159 (69.4)	179 (67.5)	442 (61.6)
Metabolism and Nutrition Disorders	153 (66.8)	156 (58.9)	418 (58.2)
Hypertriglyceridaemia	93 (40.6)	78 (29.4)	210 (29.2)
Hyperuricaemia	52 (22.7)	58 (21.9)	142 (19.8)
Hypoalbuminaemia	48 (21.0)	50 (18.9)	112 (15.6)
Decreased Appetite	31 (13.5)	43 (16.2)	100 (13.9)
Hypoproteinaemia	25 (10.9)	39 (14.7)	96 (13.4)
Hypocalcaemia	30 (13.1)	39 (14.7)	86 (12.0)
Hypercholesterolaemia	29 (12.7)	25 (9.4)	72 (10.0)
Vascular Disorders	149 (65.1)	164 (61.9)	395 (55.0)
Hypertension	148 (64.6)	159 (60.0)	386 (53.8)

Summary of ADRs for Analysis Set 1 and 2 are seen in table 67 and 68, respectively. The MAH has provided the source table for the Table 2 in Section 4.8 of the proposed SmPC.

Serious adverse events, deaths, and other significant events

SAEs:

Table 69. Summary of Serious Treatment-Emergent Adverse Events Occurring in More Than 1 Subject Receiving Surufatinib by System Organ Class, Preferred Term – Analysis Set 1

	SANET-p		SANET-ep		Total	
	Surufatinib (N = 119) n (%)	Placebo (N = 60) n (%)	Surufatinib (N = 144) n (%)	Placebo (N = 73) n (%)	Surufatinib (N = 263) n (%)	Placebo (N = 133) n (%)
Patients With Any Serious TEAE[a]	**33 (27.7)**	**10 (16.7)**	**37 (25.7)**	**14 (19.2)**	**70 (26.6)**	**24 (18.0)**
Gastrointestinal Disorders	11 (9.2)	3 (5.0)	9 (6.3)	3 (4.1)	20 (7.6)	6 (4.5)
Gastrointestinal Haemorrhage	2 (1.7)	0	2 (1.4)	0	4 (1.5)	0
Abdominal Pain	1 (0.8)	0	2 (1.4)	1 (1.4)	3 (1.1)	1 (0.8)
Ascites	2 (1.7)	0	1 (0.7)	0	3 (1.1)	0
Intestinal Obstruction	1 (0.8)	1 (1.7)	2 (1.4)	1 (1.4)	3 (1.1)	2 (1.5)
Diarrhoea	2 (1.7)	0	0	0	2 (0.8)	0
Pancreatitis	1 (0.8)	0	1 (0.7)	1 (1.4)	2 (0.8)	1 (0.8)
Vomiting	2 (1.7)	0	0	0	2 (0.8)	0
Hepatobiliary Disorders	4 (3.4)	0	5 (3.5)	2 (2.7)	9 (3.4)	2 (1.5)
Liver Injury	2 (1.7)	0	1 (0.7)	0	3 (1.1)	0
Drug-Induced Liver Injury	2 (1.7)	0	0	1 (1.4)	2 (0.8)	1 (0.8)
Hepatic Function Abnormal	1 (0.8)	0	1 (0.7)	0	2 (0.8)	0
Jaundice Cholestatic	0	0	2 (1.4)	1 (1.4)	2 (0.8)	1 (0.8)

Table 70. Summary of Serious Treatment-Emergent Adverse Events Occurring in More Than 1 Subject Receiving Surufatinib by System Organ Class, Preferred Term – Analysis Set 2

System Organ Class Preferred Term	pNET Surufatinib (N = 229) n (%)	epNET Surufatinib (N = 265) n (%)	Surufatinib ≥300 mg Daily (N = 718) n (%)
Patients with Any Serious TEAE[a]	**65 (28.4)**	**83 (31.3)**	**222 (30.9)**
Gastrointestinal Disorders	19 (8.3)	27 (10.2)	63 (8.8)
Intestinal Obstruction	2 (0.9)	6 (2.3)	9 (1.3)
Abdominal Pain	1 (0.4)	5 (1.9)	8 (1.1)
Gastrointestinal Haemorrhage	4 (1.7)	2 (0.8)	8 (1.1)
Upper Gastrointestinal Haemorrhage	2 (0.9)	2 (0.8)	7 (1.0)
Ascites	2 (0.9)	2 (0.8)	6 (0.8)
Diarrhoea	2 (0.9)	1 (0.4)	4 (0.6)
Pancreatitis	1 (0.4)	2 (0.8)	4 (0.6)
Ileus	0	2 (0.8)	3 (0.4)
Vomiting	3 (1.3)	0	3 (0.4)
Abdominal Distension	1 (0.4)	0	2 (0.3)
Abdominal Pain Upper	1 (0.4)	1 (0.4)	2 (0.3)
Small Intestinal Obstruction	0	0	2 (0.3)
Hepatobiliary Disorders	6 (2.6)	11 (4.2)	31 (4.3)
Hepatic Function Abnormal	3 (1.3)	3 (1.1)	11 (1.5)
Jaundice Cholestatic	0	5 (1.9)	8 (1.1)
Bile Duct Obstruction	0	0	3 (0.4)
Liver Injury	2 (0.9)	1 (0.4)	3 (0.4)
Cholecystitis	0	1 (0.4)	2 (0.3)
Drug-Induced Liver Injury	2 (0.9)	0	2 (0.3)

Analysis Set 1 and 2 are seen in Table 69 and 70, respectively. The 2 tables are shown only with any grade SAEs and are not directly comparable as the SAEs chosen are not the same for the 2 tables.

SAEs were common during treatment (any grades 26.6% in Analysis Set 1 and 30.9% in Analysis Set 2) and most often related to gastrointestinal and hepatobiliary disorders (7.6% and 3.4% in Analysis Set 1 and 8.8% and 4.3%, respectively). From source Table 2.7.4.4.8.1 (Analysis Set 1) concerning the high-grade events (Grade ≥3) the 2 SOCs mentioned above contribute for 6.5% and 3.0%, respectively. From source 2.7.4.4.8.2 (Analysis Set 2) they contribute for 7.4% and 4.2%,

respectively, i.e. the most common SAEs were high-grade events. The other SAEs were generally small in numbers.

Table 71. Summary of Serious Treatment-Emergent Adverse Events Occurring in ≥2 Patients Receiving Surufatinib by System Organ Class, Preferred Term – Analysis Set 1 and Analysis Set 2.

	Analysis Set 1				Analysis Set 2	
	Surufatinib (N=263) n (%)		Placebo (N=133) n (%)		Surufatinib ≥300 mg Daily (N=718) n (%)	
SOC PT	Any Grade	NCI CTC Grade ≥3	Any Grade	NCI CTC Grade ≥3	Any Grade	NCI CTC Grade ≥3
Gastrointestinal disorders	20 (7.6)	17 (6.5)	5 (3.8)	5 (3.8)	55 (7.7)	46 (6.4)
Intestinal obstruction	3 (1.1)	2 (0.8)	2 (1.5)	2 (1.5)	9 (1.3)	8 (1.1)
Abdominal pain	3 (1.1)	3 (1.1)	1 (0.8)	1 (0.8)	8 (1.1)	7 (1.0)
Gastrointestinal hemorrhage	4 (1.5)	4 (1.5)	0	0	8 (1.1)	7 (1.0)
Upper gastrointestinal hemorrhage	0	0	1 (0.8)	1 (0.8)	7 (1.0)	5 (0.7)
Ascites	3 (1.1)	2 (0.8)	0	0	6 (0.8)	4 (0.6)
Diarrhoea	2 (0.8)	2 (0.8)	0	0	4 (0.6)	4 (0.6)

	Analysis Set 1				Analysis Set 2	
	Surufatinib (N=263) n (%)		Placebo (N=133) n (%)		Surufatinib ≥300 mg Daily (N=718) n (%)	
SOC PT	Any Grade	NCI CTC Grade ≥3	Any Grade	NCI CTC Grade ≥3	Any Grade	NCI CTC Grade ≥3
Pancreatitis	2 (0.8)	2 (0.8)	1 (0.8)	1 (0.8)	4 (0.6)	4 (0.6)
Ileus	1 (0.4)	0	0	0	3 (0.4)	2 (0.3)
Vomiting	2 (0.8)	2 (0.8)	0	0	3 (0.4)	3 (0.4)
Abdominal distension	1 (0.4)	1 (0.4)	0	0	2 (0.3)	1 (0.1)
Abdominal pain upper	1 (0.4)	1 (0.4)	0	0	2 (0.3)	2 (0.3)
Small intestinal obstruction	0	0	0	0	2 (0.3)	2 (0.3)
Hepatobiliary disorders	9 (3.4)	8 (3.0)	2 (1.5)	2 (1.5)	28 (3.9)	27 (3.8)
Hepatic function abnormal	2 (0.8)	1 (0.4)	0	0	11 (1.5)	10 (1.4)
Jaundice cholestatic	2 (0.8)	2 (0.8)	1 (0.8)	1 (0.8)	8 (1.1)	8 (1.1)
Bile duct obstruction	0	0	0	0	3 (0.4)	3 (0.4)
Liver injury	3 (1.1)	3 (1.1)	0	0	3 (0.4)	3 (0.4)
Cholecystitis	1 (0.4)	1 (0.4)	0	0	2 (0.3)	2 (0.3)
Drug-induced liver injury	2 (0.8)	2 (0.8)	1 (0.8)	1 (0.8)	2 (0.3)	2 (0.3)
Renal and urinary disorders	6 (2.3)	3 (1.1)	0	0	19 (2.6)	12 (1.7)
Proteinuria	5 (1.9)	3 (1.1)	0	0	9 (1.3)	6 (0.8)
Acute kidney injury	1 (0.4)	0	0	0	7 (1.0)	4 (0.6)
Haematuria	0	0	0	0	3 (0.4)	2 (0.3)
Infections and infestations	3 (1.1)	2 (0.8)	2 (1.5)	1 (0.8)	14 (1.9)	12 (1.7)
Pneumonia	1 (0.4)	1 (0.4)	1 (0.8)	0	6 (0.8)	5 (0.7)
Biliary tract infection	1 (0.4)	1 (0.4)	0	0	3 (0.4)	3 (0.4)
Sepsis	0	0	0	0	3 (0.4)	3 (0.4)
Gastroenteritis	1 (0.4)	0	1 (0.8)	1 (0.8)	2 (0.3)	1 (0.1)
General disorders and administration site conditions	4 (1.5)	2 (0.8)	1 (0.8)	0	13 (1.8)	9 (1.3)
Death	1 (0.4)	1 (0.4)	0	0	5 (0.7)	5 (0.7)
Asthenia	2 (0.8)	1 (0.4)	1 (0.8)	0	3 (0.4)	1 (0.1)
Disease progression	0	0	0	0	2 (0.3)	2 (0.3)
Oedema peripheral	1 (0.4)	0	0	0	2 (0.3)	1 (0.1)
Pyrexia	1 (0.4)	0	0	0	2 (0.3)	0
Blood and lymphatic system disorders	5 (1.9)	4 (1.5)	0	0	10 (1.4)	8 (1.1)
Anaemia	2 (0.8)	2 (0.8)	0	0	6 (0.8)	5 (0.7)
Bone marrow failure	1 (0.4)	0	0	0	2 (0.3)	1 (0.1)
Disseminated intravascular coagulation	2 (0.8)	2 (0.8)	0	0	2 (0.3)	2 (0.3)
Investigations	2 (0.8)	2 (0.8)	0	0	9 (1.3)	8 (1.1)
Blood bilirubin increased	0	0	0	0	6 (0.8)	5 (0.7)
Platelet count decreased	2 (0.8)	2 (0.8)	0	0	3 (0.4)	3 (0.4)
Respiratory, thoracic, and mediastinal disorders	1 (0.4)	0	1 (0.8)	0	9 (1.3)	4 (0.6)
Pleural effusion	1 (0.4)	0	1 (0.8)	0	6 (0.8)	1 (0.1)
Pneumonitis	0	0	0	0	3 (0.4)	3 (0.4)
Metabolism and nutrition disorders	2 (0.8)	2 (0.8)	1 (0.8)	1 (0.8)	7 (1.0)	5 (0.7)
Hypokalaemia	2 (0.8)	2 (0.8)	0	0	3 (0.4)	3 (0.4)
Hyponatraemia	0	0	1 (0.8)	1 (0.8)	2 (0.3)	1 (0.1)
Metabolic acidosis	0	0	0	0	2 (0.3)	1 (0.1)
Cardiac disorders	2 (0.8)	1 (0.4)	0	0	6 (0.8)	4 (0.6)
Pericardial effusion	2 (0.8)	1 (0.4)	0	0	4 (0.6)	3 (0.4)

	Analysis Set 1				Analysis Set 2	
	Surufatinib (N=263) n (%)		Placebo (N=133) n (%)		Surufatinib ≥300 mg Daily (N=718) n (%)	
SOC PT	Any Grade	NCI CTC Grade ≥3	Any Grade	NCI CTC Grade ≥3	Any Grade	NCI CTC Grade ≥3
Cardiac failure	0	0	0	0	2 (0.3)	1 (0.1)
Vascular disorders	4 (1.5)	4 (1.5)	0	0	6 (0.8)	6 (0.8)
Hypertension	4 (1.5)	4 (1.5)	0	0	6 (0.8)	6 (0.8)
Nervous system disorders	3 (1.1)	3 (1.1)	0	0	5 (0.7)	5 (0.7)
Cerebral hemorrhage	3 (1.1)	3 (1.1)	0	0	5 (0.7)	5 (0.7)
Musculoskeletal and connective tissue disorders	2 (0.8)	0	0	0	4 (0.6)	1 (0.1)
Bone pain	2 (0.8)	0	0	0	2 (0.3)	0
Intervertebral disc protrusion	0	0	0	0	2 (0.3)	1 (0.1)
Neoplasm benign, malignant, and unspecified (incl cysts and polyps)	0	0	0	0	3 (0.4)	3 (0.4)
Malignant neoplasm progression	0	0	0	0	3 (0.4)	3 (0.4)
Source: Table 2.7.4.4.33.1						

Table 71 shows the summary of Serious TEAEs occurring in ≥2% of patients. Of the gastrointestinal disorders observed (7.6%) in the Surufatinib treated patients 6.5% were of Grade ≥3. All patients with gastrointestinal hemorrhage experienced Grade≥3 (1.5%). Also, most of the patients experiencing hepatobiliary disorders (3.4%) had Grade≥3 (3.0%). Proteinuria was observed in 1.9% with 1.1% having Grade≥3. The number of SAEs observed were consistent with what was found in Analysis Set 2. The other SAEs were generally small in numbers.

Table 72. Summary of Treatment-Emergent Adverse Events Leading to Death by System Organ Class, Preferred Term – Analysis Set 1

Deaths:

System Organ Class Preferred Term	SANET-p		SANET-ep		Total	
	Surufatinib (N = 119) n (%)	Placebo (N = 60) n (%)	Surufatinib (N = 144) n (%)	Placebo (N = 73) n (%)	Surufatinib (N = 263) n (%)	Placebo (N = 133) n (%)
Patients with Any TEAE Leading to Death[a]	**4 (3.4)**	**2 (3.3)**	**3 (2.1)**	**1 (1.4)**	**7 (2.7)**	**3 (2.3)**
Nervous System Disorders	2 (1.7)	1 (1.7)	1 (0.7)	0	3 (1.1)	1 (0.8)
Brain Stem Haemorrhage	1 (0.8)	0	0	0	1 (0.4)	0
Cerebral Haemorrhage	1 (0.8)	0	0	0	1 (0.4)	0
Hepatic Encephalopathy	0	0	1 (0.7)	0	1 (0.4)	0
Coma	0	1 (1.7)	0	0	0	1 (0.8)
Blood and Lymphatic System Disorders	0	0	1 (0.7)	0	1 (0.4)	0
Disseminated Intravascular Coagulation	0	0	1 (0.7)	0	1 (0.4)	0
Gastrointestinal Disorders	1 (0.8)	0	0	0	1 (0.4)	0
Gastrointestinal Haemorrhage	1 (0.8)	0	0	0	1 (0.4)	0
General Disorders and Administration Site Conditions	0	0	1 (0.7)	0	1 (0.4)	0
Death	0	0	1 (0.7)	0	1 (0.4)	0
Hepatobiliary Disorders	0	0	1 (0.7)	0	1 (0.4)	0
Liver Injury	0	0	1 (0.7)	0	1 (0.4)	0
Investigations	1 (0.8)	0	0	0	1 (0.4)	0
Platelet Count Decreased	1 (0.8)	0	0	0	1 (0.4)	0
Metabolism and Nutrition Disorders	0	0	0	1 (1.4)	0	1 (0.8)
Cachexia	0	0	0	1 (1.4)	0	1 (0.8)
Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps)	0	1 (1.7)	0	0	0	1 (0.8)
Pancreatic Neuroendocrine Tumour	0	1 (1.7)	0	0	0	1 (0.8)
Respiratory, Thoracic, and Mediastinal Disorders	0	0	0	1 (1.4)	0	1 (0.8)
Respiratory Failure	0	0	0	1 (1.4)	0	1 (0.8)

Table 73. Summary of Treatment-Emergent Adverse Events Leading to Death by System Organ Class, Preferred Term – Analysis Set 2

System Organ Class Preferred Term	pNET Surufatinib (N = 229) n (%)	epNET Surufatinib (N = 265) n (%)	Surufatinib ≥300 mg Daily (N = 718) n (%)
Patients with Any TEAE Leading to Death[a]	**6 (2.6)**	**5 (1.9)**	**29 (4.0)**
General Disorders and Administration Site Conditions	1 (0.4)	1 (0.4)	8 (1.1)
Death	0	1 (0.4)	5 (0.7)
Disease Progression	0	0	2 (0.3)
Multiple Organ Dysfunction Syndrome	1 (0.4)	0	1 (0.1)
Nervous System Disorders	3 (1.3)	1 (0.4)	5 (0.7)
Cerebral Haemorrhage	2 (0.9)	0	3 (0.4)
Brain Stem Haemorrhage	1 (0.4)	0	1 (0.1)
Hepatic Encephalopathy	0	1 (0.4)	1 (0.1)
Gastrointestinal Disorders	1 (0.4)	0	3 (0.4)
Gastrointestinal Haemorrhage	1 (0.4)	0	2 (0.3)
Diarrhoea	0	0	1 (0.1)
Hepatobiliary Disorders	0	1 (0.4)	3 (0.4)
Hepatic Failure	0	0	1 (0.1)
Hepatic Function Abnormal	0	0	1 (0.1)
Liver Injury	0	1 (0.4)	1 (0.1)

Seven (2.7%) patients with any TEAEs leading to death (Analysis Set 1) was seen in the surufatinib group vs 3 (2.3%) in the placebo group compared to 29 (4.0%) in Analysis Set 2 (Table 72 and 73, respectively). According to PTs for both groups more reasons for any death were seen. For the SOP "General Disorders and Administration Site Conditions" the reason for 1 patient was death. This is not understood. Under the SOP "Investigations" the reason was Platelet Count Decreased. This cannot be the direct reason for the death. Instead it should be haemorrhage/bleeding in some organ. Under the SOP "Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps)" the reason was Pancreatic Neuroendocrine Tumour. This should instead be Disease Progression. Corresponding irregularities were seen for the Analysis Set 2 (Table 16).

In the table describing the causes of deaths in 29 patients in Analysis set 2, there are five patients in the group of "death" only. These patients represent nearly one fifth of the patients, who died due to adverse events. The Applicant has described short narratives of those five cases of death. The narratives reveal that all 5 deaths were consistent with progressive disease, but all these patients died at home and the investigator did not have sufficient information to properly assess the cause of death, although in 1 case the investigator used the death certificate to indicate disease progression as the cause of death.

The Applicant clarifies in the SCS that "Each of the PTs for TEAEs leading to death was reported once" regarding Analysis Set 1 and "Each of the PTs for TEAEs leading to death was reported once with the exceptions of death reported as an AE (5 patients [0.7%]), cerebral hemorrhage (3 [0.4%]), malignant neoplasm progression (3 [0.4%]), disease progression (2 [0.3%]), and gastrointestinal hemorrhage (2 [0.3%])" regarding Analysis Set 2. In Analysis Set 1, a total of 12 grade 5 AEs were reported for 10 patients (Table 72). Two patients reported 2 TEAEs leading to death. One patient in the Placebo arm of the SANET-ep study reported fatal events of Cachexia and Respiratory failure. In addition, 1 patient in the surufatinib treatment arm of the SANET-p study reported fatal events of Disseminated intravascular coagulation and Hepatic encephalopathy. In Analysis Set 2, a total of 32

grade 5 AEs were reported for 29 patients. One of these is the patient from Analysis Set 1 who was randomized to the surufatinib treatment arm. Of the 2 additional patients, one reported fatal event of Cachexia and Metabolic acidosis while the other reported fatal events of Pneumoniaand Septic shock. Neither of these patients were enrolled in the SANET-p or SANET-ep trials.

Laboratory findings

Haemotology:

Table 74. Summary Shift Table in Haemoglobin (G/L) CTCAE Grade from Baseline to Worst Post Treatment Value

Baseline Status	Baseline Evaluable CTCAE Grade	Maximum Overall CTCAE Grade During Treatment n (%)					
		Analysis Set 1				Analysis Set 2	
		Surufatinib 300 mg QD (N=119, N1=118[a])		Placebo (N=60, N1=60[a])		Surufatinib ≥300 mg QD (N=229, N1=224[a])	
		Hypo	Hyper	Hypo	Hyper	Hypo	Hyper
		Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4
Hyper	Grade 4	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0
	Grade 1	0	0	0	0	0	0
Normal	Grade 0	0	1 (0.8)	1 (1.7)	0	2 (0.9)	0
Hypo	Grade 1	1 (0.8)	0	2 (3.3)	0	3 (1.3)	0
	Grade 2	0	0	0	0	1 (0.4)	0
	Grade 3	0	0	0	0	1 (0.4)	0
	Grade 4	0	0	0	0	0	0

In Analysis Set 1, a lower percentage of CTCAE grade 3/4 reduction in haemoglobin values occurred in subjects who received surufatinib compared with those who received placebo. In Analysis Set 2, 5.0% of patients had grade 3/4 reduction in hemoglobin.

Table 75. Summary Shift Table in Neutrophil (10^9/L) CTCAE Grade from Baseline to Worst Post Treatment Value

Baseline Status	Baseline Evaluable CTCAE Grade	Maximum Overall CTCAE Grade During Treatment n (%)					
		Analysis Set 1				Analysis Set 2	
		Surufatinib 300 mg QD (N=119, N1=118a)		Placebo (N=60, N1=60a)		Surufatinib ≥300 mg QD (N=229, N1=224a)	
		Hypo	Hyper	Hypo	Hyper	Hypo	Hyper
		Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4
Hyper	Grade 4	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0
	Grade 1	0	0	0	0	0	0
Normal	Grade 0	3 (2.5)	0	0	0	3 (1.3)	0
Hypo	Grade 1	0	0	0	0	0	0
	Grade 2	0	0	0	0	1 (0.4)	0
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0

In Analysis Set 1, 1.6% of patients who received surufatinib had CTCAE grade 3/4 reductions in neutrophil values compared with no subjects in the placebo arm. In Analysis Set 2, 2.0% of patients had grade 3/4 reductions in neutrophil value.

Table 76. Summary Shift Table in Lymphocyte (10^9/L) CTCAE Grade from Baseline to Worst Post Treatment Value

Baseline Status	Baseline Evaluable CTCAE Grade	Maximum Overall CTCAE Grade During Treatment n (%)					
		Analysis Set 1				Analysis Set 2	
		Surufatinib 300 mg QD (N=119, N1=118[a])		Placebo (N=60, N1=60[a])		Surufatinib ≥ 300 mg QD (N=229, N1=224[a])	
		Hypo	Hyper	Hypo	Hyper	Hypo	Hyper
		Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4
Hyper	Grade 4	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0
	Grade 1	0	0	0	0	0	0
Normal	Grade 0	3 (2.5)	0	1 (1.7)	0	6 (2.7)	0
Hypo	Grade 1	1 (0.8)	0	0	0	1 (0.4)	0
	Grade 2	2 (1.7)	0	1 (1.7)	0	4 (1.8)	0
	Grade 3	2 (1.7)	0	0	0	2 (0.9)	0
	Grade 4	0	0	0	0	0	0

In Analysis Set 1, a higher percentage of CTCAE grade 3/4 reductions in lymphocyte values occurred in subjects who received surufatinib (5.1%) compared with those who received placebo (3.1%). In Analysis Set 2, 6.3% of patients had grade 3/4 reductions in lymphocyte value.

Table 77. Summary Shift Table in Thrombocyte (10^9/L) CTCAE Grade from Baseline to Worst Post Treatment Value

Baseline Status	Baseline Evaluable CTCAE Grade	Maximum Overall CTCAE Grade During Treatment n (%)					
		Analysis Set 1				Analysis Set 2	
		Surufatinib 300 mg QD (N=119, N1=118[a])		Placebo (N=60, N1=60[a])		Surufatinib ≥ 300 mg QD (N=229, N1=224[a])	
		Hypo	Hyper	Hypo	Hyper	Hypo	Hyper
		Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4
Hyper	Grade 4	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0
	Grade 1	0	0	0	0	0	0
Normal	Grade 0	3 (2.5)	0	0	0	6 (2.7)	0
Hypo	Grade 1	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0

In Analysis Set 1, 1.6% of subjects who received surufatinib had CTCAE grade 3/4 reductions in platelet values compared with no subjects in the placebo arm. In Analysis Set 2, 3.0% of patients had grade 3/4 reductions in platelet value.

In summary, surufatinib induces pancytopenic adverse events. However, the numbers were small.

Chemistry:

Table 78. Summary Shift Table in Creatinine (µmol/L) CTCAE Grade from Baseline to Worst Post Treatment Value

Baseline Status	Baseline Evaluable CTCAE Grade	Maximum Overall CTCAE Grade During Treatment n (%)					
		Analysis Set 1				Analysis Set 2	
		Surufatinib 300 mg QD (N=119, N1=118[a])		Placebo (N=60, N1=60[a])		Surufatinib ≥ 300 mg QD (N=229, N1=224[a])	
		Hypo	Hyper	Hypo	Hyper	Hypo	Hyper
		Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4
Hyper	Grade 4	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0
	Grade 1	0	0	0	0	0	0
Normal	Grade 0	0	1 (0.8)	0	0	0	3 (1.3)
Hypo	Grade 1	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0

In Analysis Set 1, 0.8% of patients in the surufatinib arm had a Grade 3/4 elevated creatinine value, compared with none in the placebo arm. In Analysis Set 2, 1.3% of patients had Grade 3/4 elevated creatinine values.

Table 79. Summary Shift Table in Bilirubin (µmol/L) CTCAE Grade from Baseline to Worst Post Treatment Value

Baseline Status	Baseline Evaluable CTCAE Grade	Maximum Overall CTCAE Grade During Treatment n (%)					
		Analysis Set 1				Analysis Set 2	
		Surufatinib 300 mg QD (N=119, N1=118[a])		Placebo (N=60, N1=60[a])		Surufatinib ≥300 mg QD (N=229, N1=224[a])	
		Hypo	Hyper	Hypo	Hyper	Hypo	Hyper
		Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4
Hyper	Grade 4	0	0	0	0	0	0
	Grade 3	0	0	0	1 (1.7)	0	0
	Grade 2	0	0	0	0	0	0
	Grade 1	0	2 (1.7)	0	2 (3.3)	0	2 (0.9)
Normal	Grade 0	0	3 (2.5)	0	0	0	6 (2.7)
Hypo	Grade 1	0	0	0	0	0	
	Grade 2	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0

In Analysis Set 1, a higher percentage of Grade 3/4 elevated bilirubin values occurred in subjects who received surufatinib (4.2%) compared with those who received placebo (5.0%). In Analysis Set 2, 3.6% of patients had Grade 3/4 elevated bilirubin value.

Table 80. Summary Shift Table in Phosphate (mmol/L) CTCAE Grade from Baseline to Worst Post Treatment Value

Baseline Status	Baseline Evaluable CTCAE Grade	Maximum Overall CTCAE Grade During Treatment n (%)					
		Analysis Set 1				Analysis Set 2	
		Surufatinib 300 mg QD (N=119, N1=118[a])		Placebo (N=60, N1=60[a])		Surufatinib ≥300 mg QD (N=229, N1=221[a])	
		Hypo	Hyper	Hypo	Hyper	Hypo	Hyper
		Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4
Hyper	Grade 4	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0
	Grade 1	0	0	0	0	0	0
Normal	Grade 0	1 (0.9)	0	0	0	4 (1.8)	0
Hypo	Grade 1	0	0	0	0	0	0
	Grade 2	1 (0.9)	0	0	0	4 (1.8)	0
	Grade 3	0	0	1 (1.7)	0	0	0
	Grade 4	0	0	0	0	0	0

In Analysis Set 1, a higher percentage of Grade 3/4 low phosphate values occurred in subjects who received surufatinib (1.8%) compared with those who received placebo (1.7%). In Analysis Set 2, 3.6% of patients had Grade 3/4 low phosphate value.

Table 81. Summary Shift Table in Triglyceride (mmol/L) CTCAE Grade from Baseline to Worst Post Treatment Value

Baseline Status	Baseline Evaluable CTCAE Grade	Maximum Overall CTCAE Grade During Treatment n (%)					
		Analysis Set 1				Analysis Set 2	
		Surufatinib 300 mg QD (N=119, N1=118[a])		Placebo (N=60, N1=60[a])		Surufatinib ≥300 mg QD (N=229, N1=216[a])	
		Hypo	Hyper	Hypo	Hyper	Hypo	Hyper
		Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4	Grade 3/4
Hyper	Grade 4	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	3 (1.4)
	Grade 1	0	0	0	0	0	10 (4.6)
Normal	Grade 0	0	6 (5.1)	0	0	0	13 (6.0)
Hypo	Grade 1	0	6 (5.1)	0	0	0	
	Grade 2	0	2 (1.7)	0	0	0	
	Grade 3	0	0	0	0	0	0
	Grade 4	0	0	0	0	0	0

In Analysis Set 1, 11.9% of patients in the surufatinib arm had Grade 3/4 elevated triglyceride values, compared with none in the placebo arm. In Analysis Set 2, 12.0% of patients had Grade 3/4 elevated triglyceride values.

In summary, most patients experiencing Grade 3/4 were patients having grade 1 or normal values at baseline. However, the numbers were small except for elevated triglyceride.

Table 82. Summary of Postbaseline Clinically Notable Abnormality in ECG – Analysis Set 1

ECG changes:

Criteria	SANET-p		SANET-ep		Total	
	Surufatinib (N = 119) n (%)	Placebo (N = 60) n (%)	Surufatinib (N = 144) n (%)	Placebo (N = 73) n (%)	Surufatinib (N = 263) n (%)	Placebo (N = 133) n (%)
QTcF value > 450 msec to ≤ 480 msec	10 (8.4)	2 (3.3)	14 (9.7)	4 (5.5)	24 (9.1)	6 (4.5)
QTcF value > 480 msec to ≤ 500 msec	3 (2.5)	1 (1.7)	6 (4.2)	0	9 (3.4)	1 (0.8)
QTcF value > 500 msec	4 (3.4)	0	3 (2.1)	1 (1.4)	7 (2.7)	1 (0.8)
QTcF value change from baseline > 30 msec to ≤ 60 msec	33 (27.7)	13 (21.7)	43 (29.9)	20 (27.4)	76 (28.9)	33 (24.8)
QTcF value change of from baseline > 60 msec	11 (9.2)	1 (1.7)	14 (9.7)	4 (5.5)	25 (9.5)	5 (3.8)

Table 83. Summary of Postbaseline Clinically Notable Abnormality in ECG – Analysis Set 1

Criteria	SANET-p		SANET-ep		Total	
	Surufatinib (N = 119) n (%)	Placebo (N = 60) n (%)	Surufatinib (N = 144) n (%)	Placebo (N = 73) n (%)	Surufatinib (N = 263) n (%)	Placebo (N = 133) n (%)
PR interval value < 120 msec	9 (7.6)	9 (15.0)	23 (16.0)	9 (12.3)	32 (12.2)	18 (13.5)
PR interval value > 210 msec	2 (1.7)	2 (3.3)	7 (4.9)	3 (4.1)	9 (3.4)	5 (3.8)
QRS complex value > 110 msec	21 (17.6)	9 (15.0)	22 (15.3)	7 (9.6)	43 (16.3)	16 (12.0)

ECG=electrocardiogram; n = the number of subjects; N = number of subjects in the treatment group analysis set; PR=pulse rate; QRS=Q, R, and S waves of ECG; QTcF=heart rate-corrected QT interval corrected using Fridericia's formula; SANET-ep=surufatinib in advanced neuroendocrine tumors-extra-pancreatic; SANET-p=surufatinib in advanced neuroendocrine tumors-pancreatic.

Source: Table 2.7.4.9.1

Table 84. Summary of Postbaseline Clinically Notable Abnormality in ECG – Analysis Set 2

Criteria	pNET Surufatinib (N = 229) n (%)	epNET Surufatinib (N = 265) n (%)	Surufatinib ≥300 mg Daily (N = 718) n (%)
QTcF value > 450 msec to ≤ 480 msec	20 (8.7)	28 (10.6)	71 (9.9)
QTcF value > 480 msec to ≤ 500 msec	6 (2.6)	8 (3.0)	16 (2.2)
QTcF value > 500 msec	4 (1.7)	4 (1.5)	11 (1.5)
QTcF value change from baseline > 30 msec to ≤ 60 msec	54 (23.6)	72 (27.2)	162 (22.6)
QTcF value change of from baseline > 60 msec	18 (7.9)	21 (7.9)	49 (6.8)
PR interval value < 120 msec	22 (9.6)	32 (12.1)	67 (9.3)
PR interval value > 210 msec	8 (3.5)	20 (7.5)	37 (5.2)
QRS complex value > 110 msec	36 (15.7)	38 (14.3)	93 (13.0)

ECG=electrocardiogram; epNET=neuroendocrine tumors of extra-pancreatic origin; n=the number of subjects; N=number of subjects in the treatment group analysis set; pNET=neuroendocrine tumors of pancreatic origin; PR=pulse rate; QRS=Q, R, and S waves of ECG; QTcF=heart rate-corrected QT interval corrected using Fridericia's formula;

Source: Table 2.7.4.9.2

Summary of postbaseline clinically notable abnormality in ECG can be seen for Analysis Set 1 and 2 in Table 83 and 84, respectively. According to Fridericia's formula (QTcF) a QTc>480 msec without a medicinal explanation is considered pathological. The Applicant has divided the QTcF value in 2 intervals (value>480 msec and>500 msec) When you put the 2 intervals together the incidence for the Analysis Set 2 is 3.8% and for Analysis Set 1 it is for surufatinib and placebo 6.1% vs 1.5%, respectively. QTcF value change from baseline>30 msec in Analysis Set 1 is for surufatinib and placebo 38.4% and 28.6%, respectively and for >60 msec it is significantly higher for surufatinib compared to placebo (9.5% and 3.8%, respectively).

The risk of QTc prolongation has already thoroughly been discussed in Q171.

In vitro biomarker test for patient selection for safety

Not applicable.

Safety in special populations

Age:

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)
Total AEs				
Serious AEs – Total				
- Fatal				
- Hospitalization/prolong existing hospitalization				
- Life-threatening				
- Disability/incapacity				
- Other (medically significant)				
AE leading to drop-out				
Psychiatric disorders				
Nervous system disorders				
Accidents and injuries				
Cardiac disorders				
Vascular disorders				
Cerebrovascular disorders				
Infections and infestations				
Anticholinergic syndrome				
Quality of life decreased				
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures				
<other AE appearing more frequently in older patients>				

The MAH is asked to fill out the table above

SAEs Grade ≥3, TEAEs leading to interruption, reduction, treatment discontinuation or death, followed by the AESIs for the following age groups: <65 years, 65-74 years, and 74-85 years. (Tables 85-86). Summary tables for elderly age groups are provided in tables 87-88:

Table 85.

Overview of TEAEs by Age Group (<65, 65-74, 74-85) - Analysis Set 1

	Age <65 n (%)		Age 65-74 n (%)		Age 75-84 n (%)	
	Suru N=229	Placebo N=111	Suru N=33	Placebo N=20	Suru N=1	Placebo N=2
At least one TEAE	226 (98.7)	107 (96.4)	31 (93.9)	19 (95.0)	1 (100)	2 (100)
TEAEs Grade ≥3	170 (74.2)	41 (36.9)	26 (78.8)	6 (30.0)	1 (100)	0
Serious TEAEs	57 (24.9)	21 (18.9)	13 (39.4)	3 (15.0)	0	0
Serious TEAEs Grade >=3	44 (19.2)	15 (13.5)	11 (33.3)	2 (10.0)	0	0
TEAE - Dose Interruptions	106 (46.3)	32 (28.8)	18 (54.5)	6 (30.0)	0	1 (50.0)
TEAE - Dose Reductions	99 (43.2)	7 (6.3)	13 (39.4)	2 (10.0)	1 (100)	0
TEAE - Dose Interruption or Reduction	152 (66.4)	37 (33.3)	23 (69.7)	6 (30.0)	1 (100)	1 (50.0)
TEAE - Drug Discontinuation	37 (16.2)	8 (7.2)	7 (21.2)	1 (5.0)	0	0
TEAE - Death	6 (2.6)	3 (2.7)	1 (3.0)	0	0	0
AESI	220 (96.1)	96 (86.5)	31 (93.9)	18 (90.0)	1 (100)	2 (100)
Hepatic disorders (SMQ)	163 (71.2)	70 (63.1)	25 (75.8)	14 (70.0)	0	2 (100)
Serious TEAEs	10 (4.4)	3 (2.7)	2 (6.1)	0	0	0
TEAE - Dose Interruptions	17 (7.4)	7 (6.3)	1 (3.0)	0	0	0
TEAE - Dose Reductions	8 (3.5)	2 (1.8)	2 (6.1)	0	0	0
TEAE - Drug Discontinuation	6 (2.6)	3 (2.7)	2 (6.1)	0	0	0
TEAE - Death	2 (0.9)	0	0	0	0	0
Proteinuria (SMQ)	192 (83.8)	70 (63.1)	24 (72.7)	9 (45.0)	1 (100)	2 (100)
Serious TEAEs	4 (1.7)	0	1 (3.0)	0	0	0
TEAE - Dose Interruptions	31 (13.5)	4 (3.6)	5 (15.2)	1 (5.0)	0	0
TEAE - Dose Reductions	46 (20.1)	1 (0.9)	4 (12.1)	0	0	0
TEAE - Drug Discontinuation	7 (3.1)	1 (0.9)	2 (6.1)	0	0	0
TEAE - Death	0	0	0	0	0	0
Hypertension (SMQ)	164 (71.6)	30 (27.0)	23 (69.7)	9 (45.0)	1 (100)	0
Serious TEAEs	3 (1.3)	0	1 (3.0)	0	0	0
TEAE - Dose Interruptions	14 (6.1)	0	6 (18.2)	0	0	0
TEAE - Dose Reductions	20 (8.7)	2 (1.8)	3 (9.1)	1 (5.0)	1 (100)	0
TEAE - Drug Discontinuation	2 (0.9)	0	1 (3.0)	0	0	0
TEAE - Death	0	0	0	0	0	0
Hemorrhages, excluding labs (SMQ)	85 (37.1)	22 (19.8)	11 (33.3)	5 (25.0)	0	1 (50.0)
Serious TEAEs	8 (3.5)	2 (1.8)	3 (9.1)	0	0	0
TEAE - Dose Interruptions	11 (4.8)	3 (2.7)	0	0	0	0
TEAE - Dose Reductions	3 (1.3)	1 (0.9)	1 (3.0)	0	0	0
TEAE - Drug Discontinuation	5 (2.2)	1 (0.9)	2 (6.1)	0	0	0
TEAE - Death	3 (1.3)	0	1 (3.0)	0	0	0
Acute Renal Failure (SMQ)	3 (1.3)	1 (0.9)	2 (6.1)	0	0	0
Serious TEAEs	1 (0.4)	0	0	0	0	0
TEAE - Dose Interruptions	1 (0.4)	0	0	0	0	0
TEAE - Dose Reductions	1 (0.4)	0	0	0	0	0
TEAE - Drug Discontinuation	0	0	0	0	0	0
TEAE - Death	0	0	0	0	0	0

	Age <65 n (%)		Age 65-74 n (%)		Age 75-84 n (%)	
	Suru N=229	Placebo N=111	Suru N=33	Placebo N=20	Suru N=1	Placebo N=2
Thyroid dysfunction (SMQ)	133 (58.1)	16 (14.4)	21 (63.6)	3 (15.0)	1 (100)	0
Serious TEAEs	0	0	0	0	0	0
TEAE - Dose Interruptions	0	0	0	0	0	0
TEAE - Dose Reductions	0	0	0	0	0	0
TEAE - Drug Discontinuation	1 (0.4)	0	0	0	0	0
TEAE - Death	0	0	0	0	0	0

Source: Table 2.7.4.4.1.1.2, Table 2.7.4.4.14.1.2

Table 85 (Analysis Set 1) shows the three age groups where it is possible to compare the surufatinib treated and the placebo treated patients together with the pooled safety group. The overall safety profiles were similar between the patients in the <65 years and 65-74 years age groups, albeit only very few patients were represented in the 2 oldest age groups. However, more patients treated with surufatinib in the <65 years group died due to AESIs: hepatic disorders (2 patients) and haemorrhages (3 patients). None of the placebo treated patients died due to AESIs in general. No deaths were seen in the older age groups.

Table 86.

Overview of TEAEs by Age Group (<65, 65-74, 74-85) - Analysis Set 2

	Age < 65 N = 576 n (%)	Age 65 – 74 N = 126 n (%)	Age 74 – 84 N = 15 n (%)
At least one TEAE	567 (98.4)	122 (96.8)	14 (93.3)
TEAEs Grade >=3	401 (69.6)	102 (81.0)	11 (73.3)
Serious TEAEs	167 (29.0)	50 (39.7)	4 (26.7)
Serious TEAEs Grade >=3	129 (22.4)	42 (33.3)	2 (13.3)
TEAE - Dose Interruptions	271 (47.0)	67 (53.2)	6 (40.0)
TEAE - Dose Reductions	185 (32.1)	49 (38.9)	7 (46.7)
TEAE - Dose Interruption or Reduction	356 (61.8)	86 (68.3)	8 (53.3)
TEAE - Drug Discontinuation	94 (16.3)	29 (23.0)	3 (20.0)
TEAE - Death	21 (3.6)	8 (6.3)	0
AESI	533 (92.5)	114 (90.5)	11 (73.3)
Hepatic disorders (SMQ)	393 (68.2)	78 (61.9)	6 (40.0)
Serious TEAEs	28 (4.9)	9 (7.1)	0
TEAE - Dose Interruptions	41 (7.1)	9 (7.1)	1 (6.7)
TEAE - Dose Reductions	13 (2.3)	7 (5.6)	0
TEAE - Drug Discontinuation	18 (3.1)	7 (5.6)	0
TEAE - Death	3 (0.5)	1 (0.8)	0
Proteinuria (SMQ)	428 (74.3)	79 (62.7)	7 (46.7)
Serious TEAEs	7 (1.2)	1 (0.8)	1 (6.7)
TEAE - Dose Interruptions	74 (12.8)	14 (11.1)	4 (26.7)
TEAE - Dose Reductions	88 (15.3)	21 (16.7)	3 (20.0)
TEAE - Drug Discontinuation	14 (2.4)	7 (5.6)	1 (6.7)
TEAE - Death	0	0	0
Hypertension (SMQ)	351 (60.9)	67 (53.2)	7 (46.7)
Serious TEAEs	5 (0.9)	1 (0.8)	0
TEAE - Dose Interruptions	30 (5.2)	11 (8.7)	0
TEAE - Dose Reductions	30 (5.2)	6 (4.8)	2 (13.3)
TEAE - Drug Discontinuation	6 (1.0)	1 (0.8)	0
TEAE - Death	0	0	0
Hemorrhages, excluding labs (SMQ)	188 (32.6)	47 (37.3)	2 (13.3)
Serious TEAEs	20 (3.5)	12 (9.5)	1 (6.7)
TEAE - Dose Interruptions	24 (4.2)	3 (2.4)	0
TEAE - Dose Reductions	7 (1.2)	3 (2.4)	0
TEAE - Drug Discontinuation	12 (2.1)	6 (4.8)	1 (6.7)
TEAE - Death	3 (0.5)	5 (4.0)	0
Acute Renal Failure (SMQ)	17 (3.0)	11 (8.7)	1 (6.7)
Serious TEAEs	7 (1.2)	1 (0.8)	1 (6.7)
TEAE - Dose Interruptions	4 (0.7)	1 (0.8)	1 (6.7)
TEAE - Dose Reductions	3 (0.5)	3 (2.4)	1 (6.7)
TEAE - Drug Discontinuation	0	0	0
TEAE - Death	0	0	0
Thyroid dysfunction (SMQ)	290 (50.3)	56 (44.4)	3 (20.0)
Serious TEAEs	0	0	0
TEAE - Dose Interruptions	1 (0.2)	1 (0.8)	0
TEAE - Dose Reductions	0	0	0
TEAE - Drug Discontinuation	1 (0.2)	0	0
TEAE - Death	0	0	0

Source: Table 2.7.4.4.1.2.2, Table 2.7.4.4.14.2.2

Table 86 (Analysis Set 2) shows that the overall safety profiles were somewhat different between patients in the <65 years and 65-74 years age groups. In general, the incidence of TEAEs Grade ≥3, SAEs, TEAEs leading to interruption, reduction, treatment discontinuation or death were higher in the older age group. However, most of the AESIs were more frequent in the younger age group (hepatic

disorder, proteinuria, hypertension, thyroid dysfunction). There were only few patients (15) in the oldest age group.

Table 87. Summary of Serious Treatment Emergent Adverse Events, Standardized MedDRA Queries and Grouped Preferred Terms by Elderly Age Groups – Analysis Set 1

	Age < 65 n (%)		Age 65 - 74 n (%)		Age 74 - 85 n (%)	
	Suru N = 229	Placebo N =111	Suru N = 33	Placebo N = 20	Suru N = 1	Placebo N = 2
Subjects with any serious TEAEs	57 (24.9)	21 (18.9)	13 (39.4)	3 (15.0)	0	0
Resulted in death	6 (2.6)	3 (2.7)	1 (3.0)	0	0	0
Life threatening	1 (0.4)	1 (0.9)	1 (3.0)	0	0	0
Required or prolonged hospitalization	55 (24.0)	20 (18.0)	13 (39.4)	3 (15.0)	0	0
Congenital anomaly/birth defect	1 (0.4)	0	0	0	0	0
Persistent or significant disability/incapacity	1 (0.4)	0	0	0	0	0
Other medically important serious events	5 (2.2)	0	1 (3.0)	0	0	0
AE leading to treatment discontinuation [1]	37 (16.2)	8 (7.2)	7 (21.2)	1 (5.0)	0	0
Psychiatric disorders [2]	17 (7.4)	6 (5.4)	1 (3.0)	0	0	0
Nervous system disorders [2]	73 (31.9)	18 (16.2)	7 (21.2)	3 (15.0)	1 (100)	0
Accidents/injuries	7 (3.1)	0	2 (6.1)	2 (10.0)	0	0
Cardiac disorders [2]	81 (35.4)	27 (24.3)	5 (15.2)	5 (25.0)	0	1 (50.0)
Vascular disorders [2]	161 (70.3)	29 (26.1)	19 (57.6)	9 (45.0)	1 (100)	0
Cerebrovascular disorders	7 (3.1)	0	1 (3.0)	0	0	0
Infections and infestations [2]	68 (29.7)	33 (29.7)	10 (30.3)	4 (20.0)	0	1 (50.0)
Anticholinergic syndrome	0	0	0	0	0	0
Quality of life decreased [2]	0	0	0	0	0	0
Sum of fractures, postural hypotension, falls, black-outs, syncope, dizziness, ataxia	28 (12.2)	10 (9.0)	4 (12.1)	1 (5.0)	1 (100)	0
Other AEs appearing more frequently in older patients, excluding 75-84 year age group (Difference >5%)						
Blood bilirubin increased	85 (37.1)	22 (19.8)	14 (42.4)	2 (10.0)	0	2 (100)
Oedema peripheral	31 (13.5)	5 (4.5)	10 (30.3)	2 (10.0)	0	0
Blood creatinine increased	30 (13.1)	2 (1.8)	8 (24.2)	2 (10.0)	0	0
Abdominal distension	36 (15.7)	11 (9.9)	7 (21.2)	3 (15.0)	0	0
Hyponatraemia	15 (6.6)	3 (2.7)	7 (21.2)	2 (10.0)	0	0
Pyrexia	23 (10.0)	11 (9.9)	7 (21.2)	0	0	0
Blood alkaline phosphatase increased	13 (5.7)	9 (8.1)	6 (18.2)	1 (5.0)	0	0
Hypocalcaemia	24 (10.5)	9 (8.1)	6 (18.2)	4 (20.0)	0	0
Blood uric acid increased	23 (10.0)	2 (1.8)	5 (15.2)	1 (5.0)	0	0

	Age < 65 n (%)		Age 65 - 74 n (%)		Age 74 - 85 n (%)	
	Suru N = 229	Placebo N =111	Suru N = 33	Placebo N = 20	Suru N = 1	Placebo N = 2
Hepatic function abnormal	11 (4.8)	4 (3.6)	5 (15.2)	1 (5.0)	0	0
Abdominal discomfort	16 (7.0)	10 (9.0)	4 (12.1)	1 (5.0)	0	0
Gastrointestinal haemorrhage	2 (0.9)	2 (1.8)	4 (12.1)	0	0	0
Hyperkalaemia	13 (5.7)	3 (2.7)	4 (12.1)	2 (10.0)	0	0
Hyperphospataemia	1 (0.4)	2 (1.8)	4 (12.1)	0	0	0
Hypochloraemia	9 (3.9)	3 (2.7)	4 (12.1)	0	0	0
Blood pressure increased	8 (3.5)	4 (3.6)	4 (12.1)	0	0	0
Blood urea increased	16 (7.0)	0	4 (12.1)	0	0	0
Thyroxine free increased	6 (2.6)	3 (2.7)	3 (9.1)	0	0	0
Ventricular septal defect	4 (1.7)	0	3 (9.1)	0	0	0
Diabetes mellitus	1 (0.4)	0	2 (6.1)	0	0	0
Electrocardiogram QT prolonged	2 (0.9)	2 (1.8)	2 (6.1)	0	0	0
Oliguria	1 (0.4)	0	2 (6.1)	0	0	0
Pneumonia	2 (0.9)	1 (0.9)	2 (6.1)	1 (5.0)	0	0
Respiratory failure	0	1 (0.9)	2 (6.1)	0	0	0

suru = surufatinib.
Source: [1] Table 2.7.4.4.1.1.2, [2] Table 2.7.4.4.2.1.2, Table 2.7.4.4.27.1.1

Table 88. Summary of Serious Treatment Emergent Adverse Events, Standardized MedDRA Queries and Grouped Preferred Terms by Elderly Age Groups – Analysis Set 2

	Surufatinib ≥ 300 mg daily		
	Age < 65 N = 576 n (%)	Age 65 – 74 N = 126 n (%)	Age 74 – 85 N = 15 n (%)
Subjects with any serious TEAEs	167 (29.0)	50 (39.7)	4 (26.7)
Resulted in death	20 (3.5)	8 (6.3)	0
Life threatening	5 (0.9)	4 (3.2)	0
Required or prolonged hospitalization	154 (26.7)	45 (35.7)	3 (20.0)
Congenital anomaly/birth defect	2 (0.3)	0	0
Persistent or significant disability/incapacity	2 (0.3)	0	0
Other medically important serious events	9 (1.6)	4 (3.2)	1 (6.7)
Not collected [a]	7 (1.2)	1 (0.8)	0
AE leading to treatment discontinuation [1]	94 (16.3)	29 (23.0)	3 (20.0)
Psychiatric disorders [2]	31 (5.4)	6 (4.8)	1 (6.7)
Nervous system disorders [2]	155 (26.9)	39 (31.0)	4 (26.7)
Accidents/injuries	17 (3.0)	7 (5.6)	0
Cardiac disorders [2]	189 (32.8)	25 (19.8)	2 (13.3)
Vascular disorders [2]	336 (58.3)	64 (50.8)	7 (46.7)
Cerebrovascular disorders	11 (1.9)	6 (4.8)	0
Infections and infestations [2]	163 (28.3)	47 (37.3)	4 (26.7)
Anticholinergic syndrome	0	0	0
Quality of life decreased [2]	0	0	0
Sum of fractures, postural hypotension, falls, black-outs, syncope, dizziness, ataxia	54 (9.4)	14 (11.1)	1 (6.7)
Other AEs appearing more frequently in older patients, excluding 75-84 year age group (Difference >3%)			
Oedema peripheral	86 (14.9)	33 (26.2)	5 (33.3)
Anaemia	99 (17.2)	29 (23.0)	1 (6.7)
Decreased appetite	83 (14.4)	28 (22.2)	2 (13.3)
Nausea	94 (16.3)	27 (21.4)	1 (6.7)
Platelet count decreased	89 (15.5)	27 (21.4)	3 (20.0)
Blood creatinine increased	77 (13.4)	24 (19.0)	0
Hypoproteinaemia	84 (14.6)	24 (19.0)	1 (6.7)
Vomiting	86 (14.9)	24 (19.0)	1 (6.7)
Weight decreased	63 (10.9)	21 (16.7)	0
Haematuria	52 (9.0)	20 (15.9)	1 (6.7)
Hyponatraemia	41 (7.1)	20 (15.9)	1 (6.7)
Hepatic function abnormal	35 (6.1)	13 (10.3)	1 (6.7)
Blood alkaline phosphatase increased	37 (6.4)	12 (9.5)	0
Hypochloraemia	17 (3.0)	9 (7.1)	0
Gastrointestinal haemorrhage	8 (1.4)	7 (5.6)	0
Pneumonia	7 (1.2)	7 (5.6)	0
Dehydration	5 (0.9)	5 (4.0)	0

Tables 87 and 88 show for Analysis Set 1 and 2 that the incidence of SAEs in surufatinib-treated patients was higher in the older age group compared with the younger age group. Similarly, the incidence of TEAEs leading to treatment discontinuations was also higher in the older age group. Unlike Analysis Set 1, this time the older age group did have a higher incidence of nervous system disorders, cerebrovascular disorders, infections and infestations, as well as the AE terms related to falls and fractures.

In summary, the incidence of SAEs in surufatinib-treated patients was higher in the older age groups compared with the younger age group while AESIs were more frequent in the younger age group.

Gender

Table 89. Overview of TEAEs by Gender – Analysis Set 1

	Male		Female	
	Surufatinib N=147	Placebo N=65	Surufatinib N=116	Placebo N=68
At least one TEAE all Grades	143 (97.3)	64 (98.5)	115 (99.1)	64 (94.1)
TEAEs Grade ≥3	102 (69.4)	23 (35.4)	95 (81.9)	24 (35.3)
SAEs all Grades	35 (23.8)	13 (20.0)	35 (30.2)	11 (16.2)
SAEs Grade ≥3	26 (17.7)	9 (13.8)	29 (25.0)	8 (11.8)
TEAE - Dose Interruptions	56 (38.1)	22 (33.8)	68 (58.6)	17 (25.0)
TEAE - Dose Reductions	48 (32.7)	4 (6.2)	65 (56.0)	5 (7.4)
TEAE - Drug Discontinuation	23 (15.6)	5 (7.7)	21 (18.1)	4 (5.9)
TEAE - Death	2 (1.4)	2 (3.1)	5 (4.3)	1 (1.5)
AESI	138 (93.9)	61 (93.8)	114 (98.3)	55 (80.9)
Hepatic disorders (SMQ)	99 (67.3)	46 (70.8)	89 (76.7)	40 (58.8)
SAEs	6 (4.1)	2 (3.1)	6 (5.2)	1 (1.5)
TEAE - Dose Interruptions	13 (8.8)	2 (3.1)	5 (4.3)	5 (7.4)
TEAE - Dose Reductions	7 (4.8)	1 (1.5)	3 (2.6)	1 (1.5)
TEAE - Drug Discontinuation	5 (3.4)	2 (3.1)	3 (2.6)	1 (1.5)
TEAE - Death	0	0	2 (1.7)	0
Proteinuria (SMQ)	118 (80.3)	44 (67.7)	99 (85.3)	37 (54.4)
SAEs	3 (2.0)	0	2 (1.7)	0
TEAE - Dose Interruptions	15 (10.2)	1 (1.5)	21 (18.1)	4 (5.9)
TEAE - Dose Reductions	18 (12.2)	1 (1.5)	32 (27.6)	0
TEAE - Drug Discontinuation	3 (2.0)	0	6 (5.2)	1 (1.5)
TEAE - Death	0	0	0	0
Hypertension (SMQ)	92 (62.6)	21 (32.3)	96 (82.8)	18 (26.5)
SAEs	1 (0.7)	0	3 (2.6)	0
TEAE - Dose Interruptions	5 (3.4)	0	15 (12.9)	0
TEAE - Dose Reductions	7 (4.8)	1 (1.5)	17 (14.7)	2 (2.9)
TEAE - Drug Discontinuation	3 (2.0)	0	0	0
TEAE - Death	0	0	0	0
Hemorrhages, excluding labs (SMQ)	43 (29.3)	15 (23.1)	53 (45.7)	13 (19.1)
SAEs	3 (2.0)	1 (1.5)	8 (6.9)	1 (1.5)
TEAE - Dose Interruptions	3 (2.0)	1 (1.5)	8 (6.9)	2 (2.9)
TEAE - Dose Reductions	1 (0.7)	0	3 (2.6)	1 (1.5)
TEAE - Drug Discontinuation	2 (1.4)	0	5 (4.3)	1 (1.5)
TEAE - Death	1 (0.7)	0	3 (2.6)	0
Acute Renal Failure (SMQ)	2 (1.4)	0	3 (2.6)	1 (1.5)
SAEs	0	0	1 (0.9)	0
TEAE - Dose Interruptions	0	0	1 (0.9)	0
TEAE - Dose Reductions	0	0	1 (0.9)	0
TEAE - Drug Discontinuation	0	0	0	0
TEAE - Death	0	0	0	0
Thyroid dysfunction (SMQ)	68 (46.3)	7 (10.8)	87 (75.0)	12 (17.6)
SAEs	0	0	0	0
TEAE - Dose Interruptions	0	0	0	0
TEAE - Dose Reductions	0	0	0	0
TEAE - Drug Discontinuation	0	0	1 (0.9)	0
TEAE - Death	0	0	0	0

Table 90. Overview of TEAEs by Gender – Analysis Set 2

	Male N=389 n (%)	Female N=329 n (%)
At least one TEAE all Grades	382 (98.2)	322 (97.9)
TEAEs Grade ≥3	255 (65.6)	260 (79.0)
SAEs all Grades	108 (27.8)	114 (34.7)
SAEs Grade ≥3	83 (21.3)	91 (27.7)
TEAE - Dose Interruptions	166 (42.7)	178 (54.1)
TEAE - Dose Reductions	105 (27.0)	136 (41.3)
TEAE - Drug Discontinuation	58 (14.9)	69 (21.0)
TEAE - Death	12 (3.1)	17 (5.2)
AESI	353 (90.7)	306 (93.0)
Hepatic disorders (SMQ)	253 (65.0)	224 (68.1)
SAEs	19 (4.9)	18 (5.5)
TEAE - Dose Interruptions	27 (6.9)	24 (7.3)
TEAE - Dose Reductions	9 (2.3)	11 (3.3)
TEAE - Drug Discontinuation	16 (4.1)	9 (2.7)
TEAE - Death	2 (0.5)	2 (0.6)
Proteinuria (SMQ)	274 (70.4)	240 (72.9)
SAEs	4 (1.0)	5 (1.5)
TEAE - Dose Interruptions	40 (10.3)	52 (15.8)
TEAE - Dose Reductions	49 (12.6)	63 (19.1)
TEAE - Drug Discontinuation	10 (2.6)	12 (3.6)
TEAE - Death	0	0
Hypertension (SMQ)	217 (55.8)	209 (63.5)
SAEs	2 (0.5)	5 (1.5)
TEAE - Dose Interruptions	11 (2.8)	30 (9.1)
TEAE - Dose Reductions	14 (3.6)	24 (7.3)
TEAE - Drug Discontinuation	6 (1.5)	2 (0.6)
TEAE - Death	0	0
Hemorrhages, excluding labs (SMQ)	109 (28.0)	128 (38.9)
SAEs	10 (2.6)	23 (7.0)
TEAE - Dose Interruptions	12 (3.1)	15 (4.6)
TEAE - Dose Reductions	3 (0.8)	7 (2.1)
TEAE - Drug Discontinuation	5 (1.3)	14 (4.3)
TEAE - Death	2 (0.5)	6 (1.8)
Acute Renal Failure (SMQ)	13 (3.3)	16 (4.9)
SAEs	2 (0.5)	7 (2.1)
TEAE - Dose Interruptions	1 (0.3)	5 (1.5)
TEAE - Dose Reductions	3 (0.8)	4 (1.2)
TEAE - Drug Discontinuation	0	0
TEAE - Death	0	0
Thyroid dysfunction (SMQ)	158 (40.6)	191 (58.1)
SAEs	0	0
TEAE - Dose Interruptions	0	2 (0.6)
TEAE - Dose Reductions	0	0
TEAE - Drug Discontinuation	0	1 (0.3)
TEAE - Death	0	0

Source: Table 2.7.4.4.1.2.3, Table 2.7.4.4.14.2.3

For Analysis Set 1 (Table 89) a generally higher incidence is shown in female patients by 10-20%. The largest differences were seen for TEAEs leading to interruption (58.6% in females vs 38.1% in males) and TEAEs leading to reduction (56.0% in females vs 32.7% in males). For the AESIs, the largest difference was seen for thyroid dysfunction (75.0% in females vs 46.3% in males). According to Analysis Set 2 (Table 90) a similar, albeit smaller difference is seen between female and male patients.

Race

Table 91. Overview of TEAEs by Race – Analysis Set 1

	Asian n (%)		Unknown n (%)	
	Surufatinib N=251	Placebo N=130	Surufatinib N=12	Placebo N=3
At least one TEAE all Grades	249 (99.2)	126 (96.9)	9 (75.0)	2 (66.7)
TEAEs Grade ≥3	191 (76.1)	45 (34.6)	6 (50.0)	2 (66.7)
SAEs all Grades	68 (27.1)	23 (17.7)	2 (16.7)	1 (33.3)
SAEs Grade ≥3	54 (21.5)	16 (12.3)	1 (8.3)	1 (33.3)
TEAE - Dose Interruptions	123 (49.0)	38 (29.2)	1 (8.3)	1 (33.3)
TEAE - Dose Reductions	111 (44.2)	9 (6.9)	2 (16.7)	0
TEAE - Drug Discontinuation	42 (16.7)	9 (6.9)	2 (16.7)	0
TEAE - Death	7 (2.8)	3 (2.3)	0	0
AESI	243 (96.8)	114 (87.7)	9 (75.0)	2 (66.7)
Hepatic disorders (SMQ)	186 (74.1)	84 (64.6)	2 (16.7)	2 (66.7)
SAEs	12 (4.8)	3 (2.3)	0	0
TEAE - Dose Interruptions	18 (7.2)	7 (5.4)	0	0
TEAE - Dose Reductions	10 (4.0)	2 (1.5)	0	0
TEAE - Drug Discontinuation	8 (3.2)	3 (2.3)	0	0
TEAE - Death	2 (0.8)	0	0	0
Proteinuria (SMQ)	212 (84.5)	81 (62.3)	5 (41.7)	0
SAEs	4 (1.6)	0	1 (8.3)	0
TEAE - Dose Interruptions	36 (14.3)	5 (3.8)	0	0
TEAE - Dose Reductions	48 (19.1)	1 (0.8)	2 (16.7)	0
TEAE - Drug Discontinuation	9 (3.6)	1 (0.8)	0	0
TEAE - Death	0	0	0	0
Hypertension (SMQ)	183 (72.9)	39 (30.0)	5 (41.7)	0
SAEs	4 (1.6)	0	0	0
TEAE - Dose Interruptions	19 (7.6)	0	1 (8.3)	0
TEAE - Dose Reductions	24 (9.6)	3 (2.3)	0	0
TEAE - Drug Discontinuation	2 (0.8)	0	1 (8.3)	0
TEAE - Death	0	0	0	0
Hemorrhages, excluding labs (SMQ)	93 (37.1)	28 (21.5)	3 (25.0)	0
SAEs	10 (4.0)	2 (1.5)	1 (8.3)	0
TEAE - Dose Interruptions	11 (4.4)	3 (2.3)	0	0
TEAE - Dose Reductions	4 (1.6)	1 (0.8)	0	0
TEAE - Drug Discontinuation	6 (2.4)	1 (0.8)	1 (8.3)	0
TEAE - Death	4 (1.6)	0	0	0
Acute Renal Failure (SMQ)	5 (2.0)	1 (0.8)	0	0
SAEs	1 (0.4)	0	0	0
TEAE - Dose Interruptions	1 (0.4)	0	0	0
TEAE - Dose Reductions	1 (0.4)	0	0	0
TEAE - Drug Discontinuation	0	0	0	0
TEAE - Death	0	0	0	0
Thyroid dysfunction (SMQ)	153 (61.0)	19 (14.6)	2 (16.7)	0
SAEs	0	0	0	0
TEAE - Dose Interruptions	0	0	0	0
TEAE - Dose Reductions	0	0	0	0
TEAE - Drug Discontinuation	1 (0.4)	0	0	0
TEAE - Death	0	0	0	0

Source: Table 2.7.4.4.1.1.4, Table 2.7.4.4.14.1.4

Table 92. Overview of TEAEs by Race – Analysis Set 2

	Asian N=610 n (%)	Non-Asian N=80 n (%)	Unknown N=28 n (%)
At least one TEAE all Grades	601 (98.5)	76 (95.0)	27 (96.4)
TEAEs Grade ≥3	439 (72.0)	57 (71.3)	19 (67.9)
SAEs all Grades	181 (29.7)	28 (35.0)	13 (46.4)
SAEs Grade ≥3	140 (23.0)	24 (30.0)	10 (35.7)
TEAE - Dose Interruptions	294 (48.2)	39 (48.8)	11 (39.3)
TEAE - Dose Reductions	212 (34.8)	21 (26.3)	8 (28.6)
TEAE - Drug Discontinuation	107 (17.5)	12 (15.0)	8 (28.6)
TEAE - Death	24 (3.9)	4 (5.0)	1 (3.6)
AESI	578 (94.8)	58 (72.5)	23 (82.1)
Hepatic disorders (SMQ)	441 (72.3)	22 (27.5)	14 (50.0)
SAEs	34 (5.6)	2 (2.5)	1 (3.6)
TEAE - Dose Interruptions	45 (7.4)	5 (6.3)	1 (3.6)
TEAE - Dose Reductions	18 (3.0)	2 (2.5)	0
TEAE - Drug Discontinuation	23 (3.8)	1 (1.3)	1 (3.6)
TEAE - Death	4 (0.7)	0	0
Proteinuria (SMQ)	477 (78.2)	19 (23.8)	18 (64.3)
SAEs	7 (1.1)	1 (1.3)	1 (3.6)
TEAE - Dose Interruptions	84 (13.8)	5 (6.3)	3 (10.7)
TEAE - Dose Reductions	100 (16.4)	8 (10.0)	4 (14.3)
TEAE - Drug Discontinuation	19 (3.1)	3 (3.8)	0
TEAE - Death	0	0	0
Hypertension (SMQ)	382 (62.6)	31 (38.8)	13 (46.4)
SAEs	4 (0.7)	3 (3.8)	0
TEAE - Dose Interruptions	32 (5.2)	6 (7.5)	3 (10.7)
TEAE - Dose Reductions	34 (5.6)	4 (5.0)	0
TEAE - Drug Discontinuation	5 (0.8)	2 (2.5)	1 (3.6)
TEAE - Death	0	0	0
Hemorrhages, excluding labs (SMQ)	213 (34.9)	13 (16.3)	11 (39.3)
SAEs	26 (4.3)	1 (1.3)	6 (21.4)
TEAE - Dose Interruptions	25 (4.1)	0	2 (7.1)
TEAE - Dose Reductions	9 (1.5)	0	1 (3.6)
TEAE - Drug Discontinuation	14 (2.3)	0	5 (17.9)
TEAE - Death	6 (1.0)	1 (1.3)	1 (3.6)
Acute Renal Failure (SMQ)	27 (4.4)	1 (1.3)	1 (3.6)
SAEs	9 (1.5)	0	0
TEAE - Dose Interruptions	6 (1.0)	0	0
TEAE - Dose Reductions	7 (1.1)	0	0
TEAE - Drug Discontinuation	0	0	0
TEAE - Death	0	0	0
Thyroid dysfunction (SMQ)	326 (53.4)	10 (12.5)	13 (46.4)
SAEs	0	0	0
TEAE - Dose Interruptions	2 (0.3)	0	0
TEAE - Dose Reductions	0	0	0
TEAE - Drug Discontinuation	1 (0.2)	0	0
TEAE - Death	0	0	0

Source: Table 2.7.4.4.1.2.4, Table 2.7.4.4.14.2.4

As nearly all patients in the Analysis Set 1 (Table 91) were Asian with only 12 patients having unknown race, the data cannot be interpreted. For Analysis Set 2 (Table 92) the overview of TEAEs by race shows that non-Asian patients generally had similar or lower incidences compared with Asian patients. The only exceptions were for SAEs (35.0% in non-Asian vs 29.7% in Asian), SAEs Grade ≥3 (30.0% in non-Asian vs 23.0% in Asian), and TEAEs leading to death (5.0% in non-Asian vs 3.9% in Asian). This most likely reflects the generally older patients in the non-Asian population. However, the overall TEAEs and AESIs were less frequent in the non-Asian patients.

Immunological events

Not applicable.

Safety related to drug-drug interactions and other interactions

Effect of Other Drugs on Surufatinib:

In the clinical studies of surufatinib that have been conducted, no drug interaction events were reported, although strong CYP3A4 inhibitors were prohibited. A clinical study of the drug-drug interaction (DDI) between surufatinib and the strong CYP3A inhibitor itraconazole (Study 2019 012 00US2) showed that itraconazole increased the systemic surufatinib exposure following a single 200 mg surufatinib dose by approximately 2-fold (Module 2.7.2, Section 2.4.2.1). Based on physiologically based PK (PBPK) modeling, fluconazole, a moderate CYP3A4 inhibitor, resulted in geometric mean ratios (GMRs) for surufatinib Cmax and area under the plasma concentration-time curve (AUC) of 1.46 and 1.75, respectively, and cimetidine, a weak CYP3A4 inhibitor, resulted in GMRs for surufatinib Cmax and AUC of 1.11 and 1.12, respectively (Module 2.7.2, Section 2.4.2.4). The results based on clinical study and simulation analysis support recommendations that the dose of surufatinib should be reduced to 150 mg QD when coadministered with strong CYP3A inhibitors and to 200 mg QD when coadministered with moderate CYP3A inhibitors. No dose adjustment is necessary when surufatinib is coadministered with weak CYP3A inhibitors.

A clinical study of the DDI between surufatinib and the strong CYP3A inducer rifampin (Study 2020-012-00US1) showed that rifampin decreased surufatinib exposure by 62% to 74% compared with surufatinib alone following a single 300 mg surufatinib dose (Module 2.7.2, Section 3.4.2.1.2). Based on PBPK modeling, efavirenz, a moderate CYP3A4 inducer, resulted in GMRs for surufatinib of 0.45 to 0.52 for Cmax and 0.37 to 0.42 for AUC (Module 2.7.2, Section 2.4.2.4). Dose adjustment cannot be recommended when surufatinib is used concomitantly with a CYP3A inducer because surufatinib was evaluated up to 400 mg QD only in Study 2015-012-00US1 and no PK data is available at doses of >400 mg QD. Therefore, coadministration of surufatinib with a strong or moderate CYP3A inducer should be avoided.

As surufatinib exhibits pH dependent solubility in aqueous media, acid-reducing agents such as proton-pump inhibitors may affect the solubility and absorption of surufatinib. A clinical study of the DDI between surufatinib and the proton-pump inhibitor rabeprazole (Study 2020 012 00US1) showed that rabeprazole marginally increased surufatinib systemic exposure by approximately 1.2-fold following a single 300 mg surufatinib dose (Module 2.7.2, Section 3.4.2.1.3). When coadministered with acid-reducing agents, no dose adjustment is necessary for surufatinib, but it should be taken with food.

Surufatinib is a substrate of efflux transporter P-glycoprotein (P-gp). In humans, surufatinib exhibited linear PK over the dose range of 50 to 400 mg QD and the fraction of absorption is predicted to be approximately >85%. These findings suggest that P-gp does not limit the absorption of surufatinib, and therefore inhibition or induction of P-gp is not expected to change the PK of surufatinib in a clinically relevant manner (Module 2.7.2, Section 3.4.2.1.4).

Effect of Surufatinib on Other Drugs:

In vitro, surufatinib did not induce or have reversible inhibitory effects on CYP enzymes, but did have a strong time-dependent inhibitory effect on CYP3A4/5, which may increase the in vivo exposure of concomitant drugs that have CYP3A4/5-mediated metabolism.

In vitro, surufatinib also inhibited P-gp and breast cancer resistant protein (BCRP), which may affect the oral absorption of coadministered drugs that are P-gp and/or BCRP substrates.

A PBPK model was used to predict the magnitude of the potential interactions. Simulations with the index substrate of CYP3A4 (midazolam) predicted a moderate interaction, simulations with a P-gp substrate (digoxin) predicted no clinically significant interaction, and simulations with a BCRP substrate (rosuvastatin) predicted a weak interaction (Module 2.7.2, Section 2.4.2.4).

Based on the PBPK results, patients should avoid concomitant use of medications that are sensitive substrates of CYP3A4 or substrates of CYP3A4 with narrow therapeutic index, where possible. If used together, the dose of the CYP3A4 substrate should be reduced and patients should be monitored for signs and symptoms of toxicities of the coadministered CYP3A4 substrate. No initial dose adjustment is necessary when surufatinib is coadministered with medications that are sensitive substrates of P gp or BCRP. However, consideration should be given to evaluate patients more frequently for adverse reactions of the coadministered sensitive P-gp or BCRP substrate. The potential for interactions with surufatinib and substrates of CYP3A4, P-gp or BCRP is considered as missing information in the surufatinib risk management plan (RMP) in Module 1.8.2.

Discontinuation due to adverse events

Permanent discontinuations:

Table 93. Summary of Treatment-Emergent Adverse Events Leading to Drug Discontinuation Occurring in More Than 1 Subject Receiving Surufatinib by System Organ Class, Preferred Term – Analysis Set 1

System Organ Class Preferred Term	SANET-p		SANET-ep		Total	
	Surufatinib (N = 119) n (%)	Placebo (N = 60) n (%)	Surufatinib (N = 144) n (%)	Placebo (N = 73) n (%)	Surufatinib (N = 263) n (%)	Placebo (N = 133) n (%)
Patients with Any TEAEa Leading to Drug Discontinuation	16 (13.4)	5 (8.3)	28 (19.4)	4 (5.5)	44 (16.7)	9 (6.8)
Gastrointestinal Disorders	5 (4.2)	1 (1.7)	5 (3.5)	1 (1.4)	10 (3.8)	2 (1.5)
Abdominal Pain Upper	1 (0.8)	1 (1.7)	1 (0.7)	0	2 (0.8)	1 (0.8)
Diarrhoea	0	0	2 (1.4)	0	2 (0.8)	0
Gastrointestinal Haemorrhage	1 (0.8)	0	1 (0.7)	0	2 (0.8)	0
Vomiting	2 (1.7)	0	0	0	2 (0.8)	0
Investigations	2 (1.7)	1 (1.7)	5 (3.5)	1 (1.4)	7 (2.7)	2 (1.5)
Protein Urine Present	0	0	4 (2.8)	0	4 (1.5)	0
Hepatobiliary Disorders	3 (2.5)	0	3 (2.1)	2 (2.7)	6 (2.3)	2 (1.5)
Hepatic Function Abnormal	1 (0.8)	0	1 (0.7)	0	2 (0.8)	0
Liver Injury	1 (0.8)	0	1 (0.7)	0	2 (0.8)	0
Renal and Urinary Disorders	2 (1.7)	1 (1.7)	3 (2.1)	0	5 (1.9)	1 (0.8)
Proteinuria	2 (1.7)	1 (1.7)	3 (2.1)	0	5 (1.9)	1 (0.8)
General Disorders and Administration Site Conditions	2 (1.7)	0	2 (1.4)	0	4 (1.5)	0
Oedema Peripheral	1 (0.8)	0	1 (0.7)	0	2 (0.8)	0
Nervous System Disorders	2 (1.7)	0	2 (1.4)	0	4 (1.5)	0
Cerebral Haemorrhage	1 (0.8)	0	1 (0.7)	0	2 (0.8)	0
Blood and Lymphatic System Disorders	2 (1.7)	0	1 (0.7)	0	3 (1.1)	0
Metabolism and Nutrition Disorders	1 (0.8)	0	1 (0.7)	0	2 (0.8)	0
Vascular Disorders	0	0	2 (1.4)	0	2 (0.8)	0
Hypertension	0	0	2 (1.4)	0	2 (0.8)	0

Table 94. Summary of Treatment-Emergent Adverse Events Leading to Drug Discontinuation Occurring in More Than 1 Subject Receiving Surufatinib by System Organ Class, Preferred Term – Analysis Set 2

System Organ Class Preferred Term	pNET Surufatinib (N = 229) n (%)	epNET Surufatinib (N = 265) n (%)	Surufatinib ≥300 mg Daily (N = 718) n (%)
Patients With Any TEAEa Leading To Drug Discontinuation	**30 (13.1)**	**56 (21.1)**	**127 (17.7)**
Gastrointestinal Disorders	7 (3.1)	13 (4.9)	26 (3.6)
Diarrhoea	0	5 (1.9)	6 (0.8)
Abdominal Pain Upper	1 (0.4)	2 (0.8)	4 (0.6)
Upper Gastrointestinal Haemorrhage	1 (0.4)	1 (0.4)	4 (0.6)
Gastrointestinal Haemorrhage	2 (0.9)	1 (0.4)	3 (0.4)
Abdominal Distension	1 (0.4)	0	2 (0.3)
Ascites	1 (0.4)	1 (0.4)	2 (0.3)
Vomiting	2 (0.9)	0	2 (0.3)
Hepatobiliary Disorders	4 (1.7)	8 (3.0)	19 (2.6)
Hepatic Function Abnormal	2 (0.9)	2 (0.8)	9 (1.3)
Jaundice Cholestatic	0	3 (1.1)	3 (0.4)
Hyperbilirubinaemia	0	1 (0.4)	2 (0.3)
Liver Injury	1 (0.4)	1 (0.4)	2 (0.3)
Renal and Urinary Disorders	4 (1.7)	9 (3.4)	19 (2.6)
Proteinuria	4 (1.7)	7 (2.6)	17 (2.4)
Haematuria	0	2 (0.8)	2 (0.3)
Investigations	4 (1.7)	9 (3.4)	17 (2.4)
Blood Bilirubin Increased	2 (0.9)	1 (0.4)	5 (0.7)
Protein Urine Present	1 (0.4)	4 (1.5)	5 (0.7)
Alanine Aminotransferase Increased	1 (0.4)	1 (0.4)	2 (0.3)
Aspartate Aminotransferase Increased	0	1 (0.4)	2 (0.3)
Blood Pressure Increased	1 (0.4)	0	2 (0.3)
Nervous System Disorders	3 (1.3)	3 (1.1)	12 (1.7)
Cerebral Haemorrhage	2 (0.9)	1 (0.4)	4 (0.6)
Coma	0	0	2 (0.3)
General Disorders and Administration Site Conditions	3 (1.3)	6 (2.3)	11 (1.5)
Oedema Peripheral	1 (0.4)	3 (1.1)	4 (0.6)
Blood and Lymphatic System Disorders	4 (1.7)	2 (0.8)	8 (1.1)
Anaemia	2 (0.9)	1 (0.4)	5 (0.7)
Vascular Disorders	2 (0.9)	2 (0.8)	6 (0.8)
Hypertension	2 (0.9)	2 (0.8)	5 (0.7)
Cardiac Disorders	0	2 (0.8)	5 (0.7)
Tricuspid Valve Incompetence	0	2 (0.8)	2 (0.3)
Infections and Infestations	0	2 (0.8)	4 (0.6)
Biliary Tract Infection	0	1 (0.4)	2 (0.3)

Table 95. Summary of Treatment-Emergent Adverse Events Leading to Drug Discontinuation Occurring in ≥2 Patients Receiving Surufatinib by System Organ Class, Preferred Term – Analysis Set 1 and Analysis Set 2

	Analysis Set 1				Analysis Set 2	
	Surufatinib (N=263) n (%)		Placebo (N=133) n (%)		Surufatinib ≥300 mg Daily (N=718) n (%)	
	Any Grade	NCI CTC Grade ≥3	Any Grade	NCI CTC Grade ≥3	Any Grade	NCI CTC Grade ≥3
Subjects with any TEAE leading to drug discontinuation	29 (11.0)	23 (8.7)	3 (2.3)	1 (0.8)	86 (12.0)	69 (9.6)
Gastrointestinal disorders	9 (3.4)	7 (2.7)	1 (0.8)	0	22 (3.1)	15 (2.1)
Diarrhoea	2 (0.8)	1 (0.4)	0	0	6 (0.8)	3 (0.4)
Abdominal pain upper	2 (0.8)	1 (0.4)	1 (0.8)	0	4 (0.6)	2 (0.3)
Upper gastrointestinal hemorrhage	0	0	0	0	4 (0.6)	3 (0.4)
Gastrointestinal hemorrhage	2 (0.8)	2 (0.8)	0	0	3 (0.4)	3 (0.4)
Abdominal distension	1 (0.4)	1 (0.4)	0	0	2 (0.3)	2 (0.3)
Ascites	1 (0.4)	1 (0.4)	0	0	2 (0.3)	1 (0.1)
Vomiting	2 (0.8)	2 (0.8)	0	0	2 (0.3)	2 (0.3)
Renal and urinary disorders	5 (1.9)	3 (1.1)	1 (0.8)	0	19 (2.6)	12 (1.7)
Proteinuria	5 (1.9)	3 (1.1)	1 (0.8)	0	17 (2.4)	10 (1.4)
Haematuria	0	0	0	0	2 (0.3)	2 (0.3)
Hepatobiliary disorders	5 (1.9)	5 (1.9)	1 (0.8)	1 (0.8)	16 (2.2)	15 (2.1)
Hepatic function abnormal	2 (0.8)	2 (0.8)	0	0	9 (1.3)	9 (1.3)
Jaundice cholestatic	1 (0.4)	1 (0.4)	1 (0.8)	1 (0.8)	3 (0.4)	3 (0.4)
Hyperbilirubinaemia	0	0	0	0	2 (0.3)	1 (0.1)
Liver injury	2 (0.8)	2 (0.8)	0	0	2 (0.3)	2 (0.3)
Investigations	6 (2.3)	4 (1.5)	0	0	13 (1.8)	11 (1.5)
Blood bilirubin increased	1 (0.4)	0	0	0	5 (0.7)	4 (0.6)
Protein urine present	4 (1.5)	2 (0.8)	0	0	5 (0.7)	3 (0.4)
Alanine aminotransferase increased	1 (0.4)	1 (0.4)	0	0	2 (0.3)	2 (0.3)
Aspartate aminotransferase increased	0	0	0	0	2 (0.3)	1 (0.1)
Blood pressure increased	1 (0.4)	1 (0.4)	0	0	2 (0.3)	2 (0.3)
Nervous system disorders	2 (0.8)	2 (0.8)	0	0	6 (0.8)	6 (0.8)
Cerebral hemorrhage	2 (0.8)	2 (0.8)	0	0	4 (0.6)	4 (0.6)
Coma	0	0	0	0	2 (0.3)	2 (0.3)
Blood and lymphatic system disorders	0	0	0	0	5 (0.7)	5 (0.7)
Anaemia	0	0	0	0	5 (0.7)	5 (0.7)
Vascular disorders	2 (0.8)	2 (0.8)	0	0	5 (0.7)	5 (0.7)
Hypertension	2 (0.8)	2 (0.8)	0	0	5 (0.7)	5 (0.7)
General disorders and administration site conditions	2 (0.8)	0	0	0	4 (0.6)	2 (0.3)
Oedema peripheral	2 (0.8)	0	0	0	4 (0.6)	2 (0.3)
Cardiac disorders	1 (0.4)	1 (0.4)	0	0	2 (0.3)	1 (0.1)
Tricuspid valve incompetence	1 (0.4)	1 (0.4)	0	0	2 (0.3)	1 (0.1)
Infections and infestations	0	0	0	0	2 (0.3)	2 (0.3)
Biliary tract infection	0	0	0	0	2 (0.3)	2 (0.3)

Source: Table 2.7.4.4.33.4

According to Table 95 the overall rate of TEAEs leading to treatment discontinuation is 11.0% in the surufatinib treatment group compared with 2.3% in the placebo treatment group in Analysis Set 1. However, according to table 93 it is 16.7% and 6.8%, respectively. For Analysis Set 2 it is 12.0%. According to table 94 it is however, 17.7%. The MAH has provided TEAE Grade ≥3 in the new table 95, data that were not present in the dossier at submission why it is not possible to compare the numbers. According to table 84 8.7% and 9.6% of the patients in the Analysis Set 1 and 2 experienced Grade ≥3

TEAEs, respectively. The largest frequency seen in Analysis Set 1 was gastrointestinal disorders (2.7%) and hepatobiliary disorders (1.9%).

The MAH is asked to explain why there is not consistency between tables 93, 94 and table 95**.**

Dose reductions:

Table 96. Summary of Treatment-Emergent Adverse Events Leading to Dose Reduction Occurring in ≥2 Patients Receiving Surufatinib by System Organ Class, Preferred Term – Analysis Set 1

	SANET-p		SANET-ep		Total	
	Surufatinib (N = 119) n (%)	Placebo (N = 60) n (%)	Surufatinib (N = 144) n (%)	Placebo (N = 73) n (%)	Surufatinib (N = 263) n (%)	Placebo (N = 133) n (%)
Subjects with Any TEAE[a] Leading to Dose Reduction	48 (40.3)	3 (5.0)	65 (45.1)	6 (8.2)	113 (43.0)	9 (6.8)
Renal and Urinary Disorders	18 (15.1)	0	27 (18.8)	1 (1.4)	45 (17.1)	1 (0.8)
Proteinuria	17 (14.3)	0	27 (18.8)	1 (1.4)	44 (16.7)	1 (0.8)
Vascular Disorders	11 (9.2)	1 (1.7)	12 (8.3)	2 (2.7)	23 (8.7)	3 (2.3)
Hypertension	11 (9.2)	1 (1.7)	12 (8.3)	2 (2.7)	23 (8.7)	3 (2.3)
Investigations	8 (6.7)	2 (3.3)	12 (8.3)	0	20 (7.6)	2 (1.5)
Protein urine present	2 (1.7)	0	4 (2.8)	0	6 (2.3)	0
Alanine aminotransferase increased	2 (1.7)	1 (1.7)	3 (2.1)	0	5 (1.9)	1 (0.8)
Aspartate aminotransferase increased	2 (1.7)	1 (1.7)	3 (2.1)	0	5 (1.9)	1 (0.8)
Blood bilirubin increased	2 (1.7)	0	1 (0.7)	0	3 (1.1)	0
Blood creatinine increased	2 (1.7)	0	0	0	2 (0.8)	0
Platelet count decreased	1 (0.8)	0	1 (0.7)	0	2 (0.8)	0
Gastrointestinal Disorders	6 (5.0)	0	6 (4.2)	0	12 (4.6)	0
Diarrhoea	3 (2.5)	0	0	0	3 (1.1)	0
Gingival bleeding	0	0	2 (1.4)	0	2 (0.8)	0
Nausea	2 (1.7)	0	0	0	2 (0.8)	0
General Disorders and Administration Site Conditions	6 (5.0)	0	3 (2.1)	1 (1.4)	9 (3.4)	1 (0.8)
Asthenia	3 (2.5)	0	0	0	3 (1.1)	0
Metabolism and Nutrition Disorders	2 (1.7)	0	2 (1.4)	0	4 (1.5)	0
Hypertriglyceridaemia	1 (0.8)	0	2 (1.4)	0	3 (1.1)	0
Blood and Lymphatic System Disorders	1 (0.8)	0	2 (1.4)	0	3 (1.1)	0
Anaemia	0	0	2 (1.4)	0	2 (0.8)	0

Table 97. Summary of Treatment-Emergent Adverse Events Occurring in ≥2 Patients Receiving Surufatinib ≥300 mg Daily Leading to Dose Reduction by System Organ Class, Preferred Term – Analysis Set 2

	pNET Surufatinib (N = 229) n (%)	epNET Surufatinib (N = 265) n (%)	Surufatinib ≥300 mg Daily (N = 718) n (%)
Subjects with Any TEAE[a] Leading to Dose Reduction	79 (34.5)	108 (40.8)	241 (33.6)
Renal and Urinary Disorders	36 (15.7)	46 (17.4)	108 (15.0)
Proteinuria	35 (15.3)	46 (17.4)	100 (13.9)
Acute kidney injury	0	0	4 (0.6)
Haematuria	0	0	2 (0.3)
Renal Failure	0	0	2 (0.3)
Investigations	11 (4.8)	18 (6.8)	43 (6.0)
Protein urine present	4 (1.7)	6 (2.3)	12 (1.7)
Aspartate aminotransferase increased	3 (1.3)	4 (1.5)	9 (1.3)
Alanine aminotransferase increased	2 (0.9)	3 (1.1)	6 (0.8)
Blood bilirubin increased	2 (0.9)	1 (0.4)	6 (0.8)
Platelet count decreased	1 (0.4)	3 (1.1)	6 (0.8)
Blood creatinine increased	2 (0.9)	2 (0.8)	4 (0.6)
Amylase increased	1 (0.4)	0	3 (0.4)
Blood uric acid increased	0	1 (0.4)	2 (0.3)
Vascular Disorders	15 (6.6)	18 (6.8)	38 (5.3)
Hypertension	15 (6.6)	18 (6.8)	37 (5.2)
Gastrointestinal Disorders	8 (3.5)	13 (4.9)	27 (3.8)
Diarrhoea	5 (2.2)	2 (0.8)	7 (1.0)
Nausea	2 (0.9)	1 (0.4)	6 (0.8)
Gingival bleeding	0	3 (1.1)	4 (0.6)
Vomiting	1 (0.4)	2 (0.8)	4 (0.6)
Abdominal distension	0	1 (0.4)	2 (0.3)

Table 98. Summary of Treatment-Emergent Adverse Events Leading to Dose Reduction Occurring in ≥2 Patients by System Organ Class, Preferred Term – Analysis Set 1 and Analysis Set 2.

	Analysis Set 1				Analysis Set 2	
	Surufatinib (N=263) n (%)		Placebo (N=133) n (%)		Surufatinib ≥300 mg Daily (N=718) n (%)	
	Any Grade	NCI CTC Grade ≥3	Any Grade	NCI CTC Grade ≥3	Any Grade	NCI CTC Grade ≥3
Subjects with any TEAE leading to dose reduction	101 (38.4)	70 (26.6)	7 (5.3)	6 (4.5)	217 (30.2)	146 (20.3)
Renal and urinary disorders	44 (16.7)	25 (9.5)	1 (0.8)	0	107 (14.9)	52 (7.2)
Proteinuria	44 (16.7)	25 (9.5)	1 (0.8)	0	100 (13.9)	50 (7.0)
Acute kidney injury	0	0	0	0	4 (0.6)	1 (0.1)
Haematuria	0	0	0	0	2 (0.3)	0
Renal failure	0	0	0	0	2 (0.3)	1 (0.1)
Investigations	19 (7.2)	12 (4.6)	1 (0.8)	1 (0.8)	39 (5.4)	30 (4.2)
Protein urine present	6 (2.3)	4 (1.5)	0	0	12 (1.7)	10 (1.4)
Aspartate aminotransferase increased	5 (1.9)	5 (1.9)	1 (0.8)	1 (0.8)	9 (1.3)	7 (1.0)
Alanine aminotransferase increased	5 (1.9)	4 (1.5)	1 (0.8)	1 (0.8)	6 (0.8)	5 (0.7)
Blood bilirubin increased	3 (1.1)	2 (0.8)	0	0	6 (0.8)	5 (0.7)
Platelet count decreased	2 (0.8)	0	0	0	6 (0.8)	4 (0.6)
Blood creatinine increased	2 (0.8)	0	0	0	4 (0.6)	0
Amylase increased	0	0	0	0	3 (0.4)	3 (0.4)
Blood uric acid increased	1 (0.4)	1 (0.4)	0	0	2 (0.3)	2 (0.3)
Vascular disorders	23 (8.7)	23 (8.7)	3 (2.3)	3 (2.3)	37 (5.2)	36 (5.0)
Hypertension	23 (8.7)	23 (8.7)	3 (2.3)	3 (2.3)	37 (5.2)	36 (5.0)
Gastrointestinal disorders	7 (2.7)	2 (0.8)	0	0	20 (2.8)	5 (0.7)
Diarrhoea	3 (1.1)	2 (0.8)	0	0	7 (1.0)	3 (0.4)
Nausea	2 (0.8)	0	0	0	6 (0.8)	2 (0.3)
Gingival bleeding	2 (0.8)	0	0	0	4 (0.6)	0
Vomiting	1 (0.4)	0	0	0	4 (0.6)	1 (0.1)
Abdominal distension	0	0	0	0	2 (0.3)	0
General disorders and administration site conditions	5 (1.9)	1 (0.4)	1 (0.8)	1 (0.8)	16 (2.2)	10 (1.4)
Asthenia	3 (1.1)	0	0	0	6 (0.8)	2 (0.3)
Fatigue	1 (0.4)	0	1 (0.8)	1 (0.8)	6 (0.8)	4 (0.6)
Oedema peripheral	1 (0.4)	1 (0.4)	0	0	5 (0.7)	5 (0.7)
Face oedema	0	0	0	0	2 (0.3)	2 (0.3)
Blood and lymphatic system disorders	3 (1.1)	3 (1.1)	0	0	10 (1.4)	10 (1.4)
Anaemia	2 (0.8)	2 (0.8)	0	0	5 (0.7)	5 (0.7)
Leukopenia	1 (0.4)	1 (0.4)	0	0	2 (0.3)	2 (0.3)
Neutropenia	1 (0.4)	1 (0.4)	0	0	2 (0.3)	2 (0.3)
Thrombocytopenia	0	0	0	0	2 (0.3)	2 (0.3)
Hepatobiliary disorders	2 (0.8)	2 (0.8)	0	0	6 (0.8)	4 (0.6)
Hepatic function abnormal	0	0	0	0	3 (0.4)	2 (0.3)
Hyperbilirubinaemia	1 (0.4)	1 (0.4)	0	0	3 (0.4)	1 (0.1)
Jaundice cholestatic	1 (0.4)	1 (0.4)	0	0	2 (0.3)	2 (0.3)
Metabolism and nutrition disorders	4 (1.5)	4 (1.5)	0	0	6 (0.8)	5 (0.7)

	Analysis Set 1				Analysis Set 2	
	Surufatinib (N=263) n (%)		Placebo (N=133) n (%)		Surufatinib ≥300 mg Daily (N=718) n (%)	
	Any Grade	NCI CTC Grade ≥3	Any Grade	NCI CTC Grade ≥3	Any Grade	NCI CTC Grade ≥3
Hypertriglyceridaemia	3 (1.1)	3 (1.1)	0	0	4 (0.6)	4 (0.6)
Hyperkalaemia	1 (0.4)	1 (0.4)	0	0	2 (0.3)	1 (0.1)
Nervous system disorders	1 (0.4)	0	1 (0.8)	1 (0.8)	3 (0.4)	0
Headache	1 (0.4)	0	1 (0.8)	1 (0.8)	3 (0.4)	0
Skin and subcutaneous tissue disorders	0	0	0	0	3 (0.4)	2 (0.3)
Palmar-plantar erythrodysaesthesia syndrome	0	0	0	0	3 (0.4)	2 (0.3)
Eye disorders	0	0	0	0	2 (0.3)	2 (0.3)
Eyelid oedema	0	0	0	0	2 (0.3)	2 (0.3)
Infections and infestations	1 (0.4)	1 (0.4)	0	0	2 (0.3)	2 (0.3)
Pneumonia	1 (0.4)	1 (0.4)	0	0	2 (0.3)	2 (0.3)

Source: Table 2.7.4.4.33.3

According to Table 98 the overall rate of TEAEs leading to dose reductions is 38.4% in the surufatinib treatment group compared with 5.3% in the placebo treatment group in Analysis Set 1. However, according to table 96 it is 43.0% and 6.8%, respectively. For Analysis Set 2 it is 30.2%. According to table 97 it is however, 33.6%. The majority of the TEAEs for the surufatinib treated patients and the placebo treated patients were grade ≥3 (26.6% and 20.3%, respectively). The largest frequency seen in Analysis Set 1 was proteinuria (9.5%) and hypertension (8.7%).

The MAH is asked to explain why there is no consistency between tables 96, 97 and table 98**.**

Post marketing experience

Surufatinib was approved in China on 29 December 2020. Since the approval was received after the safety cutoff date of 30 June 2020, postmarketing data are not yet available.

Table 99. Summary of Post-Marketing Adverse Reactions – 29 Dec 2020 to 28 Dec 2021

Post-marketing Adverse Reactions	Spontaneous			Solicited
System Organ Class Preferred Term	Total	Serious	Non-Serious	Serious
Gastrointestinal disorders	28	11	17	5
Nausea	5	3	2	0
Vomiting	5	2	3	1
Abdominal pain	4	3	1	2
Abdominal discomfort	2	1	1	0
Constipation	2	0	2	0
Diarrhoea	2	0	2	1
Mouth ulceration	2	0	2	0
Abdominal distension	1	0	1	0
Gastric haemorrhage	1	1	0	0
Gastric ulcer	1	1	0	0
Gastrointestinal disorder	1	0	1	0
Glossodynia	1	0	1	0
Tongue blistering	1	0	1	0
Intestinal obstruction	0	0	0	1
General disorders and administration site conditions	22	7	15	7
Asthenia	7	3	4	1
Oedema	3	0	3	0
Disease progression	2	0	2	2
Death	1	1	0	1
Discomfort	1	1	0	0
Drug ineffective	1	1	0	0
Pyrexia	1	1	0	2
Chest discomfort	1	0	1	0
Drug intolerance	1	0	1	0
Face oedema	1	0	1	0
Generalised oedema	1	0	1	0
Oedema peripheral	1	0	1	0
Physical deconditioning	1	0	1	0
Condition aggravated	0	0	0	1
Investigations	16	3	13	1
Aspartate aminotransferase increased	2	1	1	0
Blood pressure increased	2	0	2	0
Heart rate increased	2	0	2	0
Protein urine present	2	0	2	0
Alanine aminotransferase increased	1	1	0	0
White blood cell count decreased	1	1	0	0
Blood albumin decreased	1	0	1	0
Blood bilirubin increased	1	0	1	0
Neurone-specific enolase increased	1	0	1	0
Occult blood	1	0	1	0
Platelet count decreased	1	0	1	1
Weight decreased	1	0	1	0
Nervous system disorders	7	3	4	0
Somnolence	3	0	3	0
Brain oedema	1	1	0	0
Cerebral haemorrhage	1	1	0	0
Seizure	1	1	0	0
Dizziness	1	0	1	0
Blood and lymphatic system disorders	5	4	1	0
Myelosuppression	4	4	0	0
Anaemia	1	0	1	0
Metabolism and nutrition disorders	5	0	5	2
Decreased appetite	5	0	5	2
Hepatobiliary disorders	4	3	1	1

Post-marketing Adverse Reactions	Spontaneous			Solicited
System Organ Class Preferred Term	Total	Serious	Non-Serious	Serious
Biliary obstruction	1	1	0	0
Hepatic haemorrhage	1	1	0	0
Hepatotoxicity	1	1	0	0
Hepatic pain	1	0	1	0
Hepatic failure	0	0	0	1
Vascular disorders	4	1	3	1
Hypertension	3	0	3	1
Haemorrhage	1	1	0	0
Infections and infestations	3	1	2	1
Pneumonia	1	1	0	1
Nasopharyngitis	1	0	1	0
Oral herpes	1	0	1	0
Musculoskeletal and connective tissue disorders	3	0	3	0
Back pain	1	0	1	0
Muscle discomfort	1	0	1	0
Musculoskeletal chest pain	1	0	1	0
Respiratory, thoracic and mediastinal disorders	3	1	2	0
Dyspnoea	2	1	1	0
Cough	1	0	1	0
Injury, poisoning and procedural complications	2	0	2	0
Animal bite	1	0	1	0
Fall	1	0	1	0
Renal and urinary disorders	2	1	1	0
Haematuria	2	1	1	0
Cardiac disorders	1	1	0	0
Cardiac failure	1	1	0	0
Eye disorders	1	0	1	0
Eye oedema	1	0	1	0
Psychiatric disorders	1	1	0	0
Confusional state	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	1
Neoplasm progression	0	0	0	1
Skin and subcutaneous tissue disorders	0	0	0	1
Decubitus ulcer	0	0	0	1

Source: Appendix 2b Cumulative and Interval Summary Tabulation From Post-Marketing Sources

The MAH presents the post-marketing ADRs by SOC and PT by descending order of frequency based on the total spontaneous case counts in Table 86. For the AESI events the MAH provided brief patient profiles. Surufatinib obtained marketing authorization in China on 29 December 2020, and is currently marketed under the brand name of Sulanda. The first Surufatinib Periodic Benefit Risk Evaluation Report (PBRER) covering the period from 29 Dec 2020 to 28 Dec 2021 is currently being prepared. The post-marketing safety data are presented in Table 86 from both spontaneous (serious and non-serious) and solicited (serious only) sources. Solicited sources includes an ongoing postmarketing safety study in China.

The majority of the spontaneous ADRs were reported as non-serious. The most frequent postmarketing spontaneous ADRs (>2 reports) were asthenia (7 of which 3 were serious), nausea (5 of which 3 were serious), vomiting (5 of which 2 were serious), abdominal pain (4 of which 3 were serious), myelo suppression (4 of which 4 were serious), hypertension (3 of which 0 were serious), oedema (3 of which 0 were serious) and somnolence (3 of which 0 were serious).

Discussion on clinical safety

For this application, the safety of Sevsury (surufatinib) monotherapy in subjects with advanced pancreatic (p) and extra-pancreatic (ep) neuroendocrine tumours grade 1-2 is based on the 2 pivotal phase 3 placebo-controlled studies SANET-p and SANET-ep designed to evaluate the efficacy and safety of surufatinib monotherapy compared with placebo (N=396) with a total of 263 patients treated with surufatinib. The followed open-label crossover phases of the studies where patients randomized to placebo had the opportunity to be treated with surufatinib. The safety database consists of patients treated in the pivotal studies (Analysis Set 1, N=263) and patients who received at least 1 dose of ≥300 mg surufatinib from 8 monotherapy studies (Analysis Set 2, N=718) which provides the largest pooled safety experience for surufatinib-treated patients across all indications studied at the dose level applicable to the NET patient population. However, as the unblinding date is after the interim analysis dates more patients are included in the SCS than in the CSR. In Analysis Set 2 another 40 and 94 patients in SANET-p and SANET-ep, respectively were included from the phase 1 and phase 1/1b. From the open-label cross-over phases of the studies SANET-p and SANET-ep, 92 and 91 patients were included, respectively.

The median duration of study treatment in SANET-p/placebo and SANET-ep/placebo is 10.35/7.30 and 8.69/6.24 months, respectively. However, only 33.6% and 24.3% of the patients in SANET-p and SANET-ep respectively, had an exposure above 12 months. The exposure between the pivotal studies and the overall population was comparable.

Most of the patients were enrolled in China, and in the integrated safety Analysis Set 2, there were 627 Asian patients, 80 non-Asian patients and 11 patients of unknown race. In China, the median age of enrolled patients was 53 years, mean body weight was 62.86 kg, and mean BMI was 22.87 kg/m2. In contrast, the median age of patients enrolled in the US was 64 years, mean body weight was 79.93 kg, and mean BMI was 27.82 kg/m2. The incidence of TEAEs and serious TEAEs together with Drug discontinuations due to TEAEs differ remarkably between the Asian, non-Asian and the Unknown with very higher incidences for the non-Asian and Unknown compared with the Asian. The safety profile by race and age indicate that the higher incidence of SAEs in the non-Asian population in general is not being driven by the age since SAEs, drug discontinuations, deaths due to AEs had a lower incidence in those ≥65 years compared with those <65 years, in the non-Asian patients. This is more likely due to the underlying primary diagnoses.

The most frequently administered concomitant medications were unspecified herbal and traditional Chinese medicines (TCM) (53.1% of patients in safety analysis set 2). Patients treated with surufatinib used more often TCMs in order to ease adverse events than patients with placebo. This fits together with the fact, that surufatinib treated patients had more adverse events than placebo treated patients in SANET trials. However, the effects of TCM on adverse events remains unknown.

Nearly all patients in SANET-p/placebo (99.2%/96.7%) and SANET-ep/placebo (97.2%/95.2%) had at least one AE. **AEs** were reported for ≥10% of patients including for Analysis Set 1 and 2, respectively: proteinuria (68.8%/64.3%), hypertension (68.4%/54.7%), diarrhea (49.0%/45.5%), bilirubin increased (37.6%/34.5%), hypertriglyceridaemia (35.7%/30.5%). Notably 61.7% of the patients in the placebo arm had increased liver enzymes (AST or ALT), 19.5% had increased blood bilirubin and 54.9% had proteinuria which is considered unexpectedly high. Increased liver enzymes have not been met with sufficient dosing consequences even though apparently all patients included had Grade 0-1 values at study entry which is questionable as nearly all patients having had liver metastases. Despite some of the incidences of proteinuria are explained by predisposing risk factors the overall incidence remains high. Other explanations could be uncontrolled hypertension or patients in a bad condition/inadequately selected for study entry. The surufatinib treated patients had significantly more diarrhoea and abdominal pain (49% and 37.3%, respectively compared to 22.6% for both conditions in

the placebo arm). The same was seen with constipation, asthenia and fatigue where it was seen in 13.7%, 16.3% and 14.1%, respectively compared to the placebo treated patients where it was seen in 4.5%, 8.3% and 4.1%, respectively. The surufatinib treated patients seem to have a significantly worse QoL compared to patients in the placebo arm and it is not ruled out that the placebo-treated patients experienced more AEs in terms of diarrhea and abdominal pain because they may have been undertreated with SSA. We still do not agree that there is currently no evidence-based consensus supporting SSA as first line treatment for patients having Ki-67 ≤10. Therefore, the heterogenicity of the patients enrolled in the pivotal studies do not justify the treatment strategy chosen for this subgroup of patients.

The proportion of patients with **Grade ≥3 AEs** in the surufatinib treated patient groups was higher than in the placebo groups (74.9% vs 35.3%). The most common Grade ≥3 AEs by PT (≥3% of patients) were hypertension (38.8% vs 13.5%), proteinuria (14.8% vs 0.8%), hyperglyceridaemia (5.3% vs 0%) and anaemia (3.8% vs 3.0%) in the surufatinib treated patients compared to the placebo groups, respectively. These findings were consistent with the findings in Analysis Set 2. Grade 5 AEs with fatal outcome was seen in 7 (2.7%) patients compared with 3 (2.3%) in the placebo group. In the pooled population it was 4.0%.

According to the headlines in the SCS apparently the **AESIs** are hypertension, haemorrhage, hepatic disorders, proteinuria, acute renal failure and thyroid disorders. The Applicant has not considered prolonged QTc as an AESI which is not endorsed.

Eight patients in the analysis set 2 died due to a haemorrhage (3 cerebral, 1 brain stem, 2 gastrointestinal, 1 subdural, 1 hypovolemic shock). Most of the events were deemed possible related to the study drug. According to all the narratives it is evident that all patients had a medical history of hypertension, current hypertension at the time of the event, baseline CT scans of cerebral hemorrhage or infarctions, or evidence of cerebral infarctions on CT scan at the time of the event where hypertension as AE could precipitate cerebral ischemic events, i.e. these patients may have been inadequately selected as participants in this trial. Fatal outcomes were seen for 3 of 5 of the cerebral hemorrhage patients and the brain stem hemorrhage patient. Moreover, this is also in stark contrast to the MAH's assurances of adequately treatment of hypertension with anti-hypertensives which raises serious concerns about the conduct of the trial. The evaluation of hemorrhages and the discussion of the Applicant reveals the fact that fatal gastrointestinal hemorrhages caused by surufatinib cannot be prevented by any guidelines in the SmPC given the nature of very short timelines for fatal hemorrhages. Consequently, the risk of fatal gastrointestinal hemorrhages remains as the risk of fatal CNS hemorrhages due to surufatinib-induced high blood pressure, and affects the evaluation of benefit/risk -assessment of surufatinib.

SAEs were common during treatment (any grades 26.6% in Analysis Set 1 and 30.9% in Analysis Set 2) and most often related to gastrointestinal and hepatobiliary disorders (7.6% and 3.4% in Analysis Set 1 and 8.8% and 4.3%, respectively). The most common SAEs were high-grade events. The other SAEs were generally small in numbers.

Laboratory findings: In summary, surufatinib induces pancytopenic adverse events. However, the numbers were small. QTc prolonged >60 msec was seen in 9.5% in the surufatinib treated patients compared to 3.8% in the placebo arm. The MAH has provided narratives of all events and the majority of the patients experiencing QTcF change had values presenting borderline risk, occurrence >3 weeks after the last dose of surufatinib, electrolyte abnormalities or took concomitant medications with known risk of QTc prolongation. Nonetheless, the MAH is requested to reflect the risk of QTc prolongation in section 4.8 of the SmPC, especially the increased risk with concomitant electrolyte abnormalities or medications with known risk of QTc prolongation.

The incidence of AEs leading to **discontinuation of study treatment** was seen in the surufatinib total group in 16.7% compared to 6.8% in the placebo group (17.7% for Analysis Set 2). By PT gastrointestinal disorders was the most frequent cause in 3.8% vs 1.5%, respectively (3.6% for Analysis Set 2). For "protein urine present" and "proteinuria" as a whole it was the cause in 3.4% in the surufatinib treated group vs 0.8% in the placebo group (2.4% for "proteinuria" only in the Analysis Set 2). Liver injury, cerebral haemorrhage and hypertension were the cause in 0.8%, respectively.

Additional expert consultation

Not foreseen for the time being.

Assessment of paediatric data on clinical safety

N/A

Additional safety data needed in the context of a conditional MA

None

Conclusions on clinical safety

Safety assessment of surufatinib is based on pivotal studies SANET-p and SANET-ep (N=263) and the monotherapy data set from 8 studies (N=718), considering these data as appropriate to characterize its safety profile. However, only 33.6% and 24.3% of the patients in SANET-p and SANET-ep, respectively, had an exposure above 12 months and consequently long-term safety data are lacking. As expected, patients treated with surufatinib in the experimental arms of the pivotal trials had significantly more diarrhoea, abdominal pain, constipation and fatigue than the placebo group, which explains worsened QoL. Furthermore, QTc prolonged >60 msec was seen in significantly more patients in the surufatinib treated group. The Applicant has not been able to solve the problem in conveying safety results obtained from China to the Western population and the problem of unknown effects of traditional Chinese medicines on adverse events. The risk of fatal CNS hemorrhages due to surufatinib-induced high blood pressure cannot be denied, as there were 6 patients (0,8%) with an SAE of CNS vascular disorder possibly related to surufatinib treatment, four of these six patients had highly elevated BP at the time of SAE and four of these six cases had fatal outcome. The risk of fatal gastrointestinal hemorrhages caused by surufatinib exists given the nature of very short timelines for fatal hemorrhages and is confessed even by the Applicant.

Overall, safety of surufatinib for the targeted indication is not considered established.

Risk management plan

Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hepatic toxicity, haemorrhage (grade 3 and above)
Important potential risks	Renal failure, embryo-foetal and reproductive toxicity
Missing information	Use in patients with moderate hepatic impairment

Discussion on safety specification

The Applicant has listed some safety concerns.

Almost all patients experienced AEs. A substantial number of patients experienced AEs related to the hepatic, gastrointestinal, renal and cardiovascular system, e.g. QTc prolongation and increase in blood pressure.

It is noted that there was a significantly higher incidence of QTc prolongation in the surufatinib arm (QTc prolonged >60 msec: 9.5%) compared to the placebo arm (3.8%). However, QTc prolongation itself is not a particular clinical problem, it is the risks associated with QTc prolongation that are of more clinical relevance (e.g., Torsades de Pointes and sudden cardiac death). The applicant discussed the potential risks associated with the observed increase in incidence of QTc prolongation and its impact on the B/R. The risk of clinical complications of QTc-prolongation such as Torsades de Pointes or sudden cardiac death appears to be low, therefore, the impact on the B/R is considered limited and it is agreed not to include this risk as safety concern.

The study proposed in the pharmacovigilance plan for the DDI is a PK study and no information on safety will be obtained in this study, therefore, this study has been removed from the RMP. Furthermore, section 4.5 provides clinical recommendations regarding the potential risks of this DDI. No additional risk minimisation measures are warranted at this moment to minimise the risk of the DDI. Therefore, 'Drug-drug interaction (substrates of CYP3A4, p-gp, or BCRP)' seems not to qualify to be included as missing information according to the guidance in GVP V rev 2.

Regarding long-term safety, given the life expectancy of patients indicated for surufatinib and the observed safety profile, it is considered unlikely that the long-term safety profile differs from the observed safety profile and in addition would impact the B/R of the product. It is therefore acceptable not to include long-term safety as missing information in the RMP.

Conclusions on the safety specification

Having considered the data in the safety specification; the proposed list of safety concerns is acceptable.

Pharmacovigilance plan

Routine pharmacovigilance activities beyond adverse reactions reporting and signal Detection:

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are planned with surufatinib.

Additional Pharmacovigilance Activities

The following, category 3, additional pharmacovigilance activities are planned to further investigate missing information identified in this RMP:

Pharmacokinetic study in patients with moderate hepatic impairment

PK study in patients with moderate hepatic impairment

Study short name and title:

A phase 1 study to assess the effect of hepatic impairment on the PK and safety of surufatinib

Rationale and study objectives:

This study will provide data on the effect of moderate hepatic impairment on the PK and safety of surufatinib and thus address the identified missing information of use in patients with moderate hepatic impairment. The study has a primary objective of determining the effect of moderate and mild (if enrolled) hepatic impairment on the PK of surufatinib. The secondary objective is to evaluate the safety in subjects with moderate and mild (if enrolled) hepatic impairment and subjects with normal hepatic function.

Study design:

A phase 1, open-label, multicenter, single-dose, single-period, sequential study with the primary objective of determining the effect of moderate and mild hepatic impairment on the PK of surufatinib.

Study population:

Subjects with normal hepatic function, mild hepatic impairment (Child-Pugh score of 5 to 6) or moderate hepatic impairment (Child-Pugh score of 7 to 9).

Milestones:

This study is ongoing. A final report will be provided by the end of March 2023.

Ongoing and Planned Additional Pharmacovigilance Activities

Study (study short name, and title) **Status** (Planned/Ongoing)	**Summary of Objectives**	**Safety concerns Addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				

A phase 1 study to assess the effect of hepatic impairment on the PK of surufatinib On-going	Primary objective of determining the effect of moderate and mild hepatic impairment on the PK of surufatinib. The secondary objective is to evaluate the safety in subjects with moderate and mild (if enrolled) hepatic impairment and subjects with normal hepatic function.	Use in patients with moderate hepatic impairment	Final report	31/03/2023

For the other safety concerns, the applicant did not propose any additional pharmacovigilance activities. The risk of haemorrhage is a known risk of VEGFR-TKIs and a consequence of the working mechanism on angiogenesis. Increased risk of haemorrhage was observed in both non-clinical studies and the fairly large safety database. The risk of hepatotoxicity is also a known risk of VEGF-TKIs and observed in both non-clinical studies and the applicant's safety database. Appropriate risk minimisation measures are in place and no additional pharmacovigilance activities beyond routine pharmacovigilance are considered needed to further characterise the risk of haemorrhage and hepatotoxicity.

No additional pharmacovigilance activities are proposed regarding the important potential risk of renal failure and routine pharmacovigilance is considered sufficient by the applicant. The applicant proposes to use a targeted follow-up questionnaire for all potential renal injury events to ensure collection of all relevant information from spontaneous sources.

It is acknowledged that given the rarity of the disease in combination with the observed frequency of renal failure, routine pharmacovigilance activities are most suitable to further characterise the potential risk of renal failure. The use of a targeted questionnaire is part of routine pharmacovigilance. The MAH is requested to explain whether additional information is obtained with the targeted questionnaire beyond routine follow-up of adverse events. If no additional value is identified, the targeted questionnaire can be omitted**.**

The proposed pharmacovigilance plan is considered sufficient to characterize the risks of surufatinib.

The PRAC, having considered the data submitted, is of the opinion that the proposed pharmacovigilance activities are sufficient to characterize the risks of surufatinib.

There are no planned or ongoing post-authorisation efficacy studies. The need for any PAES is pending the CHMP final review.

Risk minimisation measures

Table 100. Proposal from applicant for risk minimisation measures

Safety concern	**Risk minimization measures (routine and additional)**	**Pharmacovigilance activities**
Hepatic toxicity	**Routine risk minimisation measures:** SmPC section 4.4 and 4.8: routine risk communication.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

	SmPC section 4.2, 4.4: Recommendations on dose reductions in the event of hepatic dysfunction included in SmPC section 4.2. Recommendations for liver function monitoring included in SmPC section 4.4. PL section 2 and 4 **Additional risk minimization measures:** Not Applicable	None **Additional pharmacovigilance activities:** None
Haemorrhage grade 3 and above	**Routine risk minimisation measures:** SmPC section 4.4 and 4.8: routine risk communication. SmPC section 4.2 and 4.4: Recommendations for dose adjustment in the case of bleeding events included in section 4.2. PL section 2 and 4 **Additional risk minimization measures:** Not Applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Renal failure	**Routine risk minimisation measures:** SmPC section 4.4 and 4.8: routine risk communication. SmPC section 4.2 and 4.4: Recommendations for dose adjustment in the case of proteinuria or evidence of renal failure included in section 4.2. Recommendations for monitoring of proteinuria included in SmPC section 4.4. PL section 2 and 4 **Additional risk minimization measures:** Not Applicable	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None.
Embryo-foetal and reproductive	**Routine risk minimisation activities:** SmPC section 4.6 and 5.3: Recommendation that use not recommended during pregnancy or in	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

toxicity	female patients not using contraception included in SmPC section 4.6. PL section 2 **Additional risk minimization measures:** Not Applicable	None **Additional pharmacovigilance activities:** None.
Use in patients with hepatic impairment	**Routine risk minimisation measures:** SmPC section 4.2: Recommendations on dose reductions in the event of hepatic dysfunction and statement that should be used with caution in patients with moderate hepatic impairment and should not be used in patients with severe hepatic impairment included in SmPC section 4.2. SmPC section 4.4: Recommendations for liver function monitoring PL section 2 and 4 **Additional risk minimization measures:** Not Applicable	R**outine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** A phase 1 study to assess the effect of hepatic impairment on the PK of surufatinib

Overall conclusions on risk minimisation measures

The PRAC having considered the data submitted, was of the opinion that:

The routine risk minimisation measures proposed are sufficient to minimise the risks of surufatinib.

Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.2 (dated 26 January 2022) is not yet acceptable. Details are provided in the endorsed Rapporteur assessment report and in the list of questions in section 6.3.

PRAC Outcome

On 7 April 2022, the PRAC endorsed the PRAC rapporteur's current assessment and proposed outstanding issue(s).

Pharmacovigilance

Pharmacovigilance system

It is 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 active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the {EBD} or {IBD} to determine the forthcoming Data Lock Points.> The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. <The applicant did <not> request an alignment of the PSUR cycle with the international birth date (IBD)>. <The IBD is {DD.MM.YYYY.}>.

The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD).

Non-Conformity with agreed Paediatric Investigation Plan

NA

Benefit risk assessment

Therapeutic Context

Disease or condition

The applicant for Sevsury (surufatinib) has submitted a marketing authorisation application with the intention to support the following amended indication:

> *Sevsury is indicated for use as monotherapy for the treatment of adult patients with low grade (grade 1 [G1] or intermediate grade (grade 2 [G2]) progressive neuroendocrine tumours of extrapancreatic or pancreatic origin that are unresectable locally advanced or metastatic.*

The aim of therapy is to prolong progression free survival in patients that are either treatment-naïve or pre-treated.

Available therapies and unmet medical need

Treatment options for managing locally advanced and metastatic NETs consist primarily of cytoreductive surgery, ablative procedures, and systemic antitumor therapy, including somatostatin analogs (SSAs), everolimus, sunitinib (limited to pNETs only), 177Lu-DOTATATE (widely used but approval limited to G1-2 gastroenteropancreatic NETs), interferon-alpha (although approved for 'carcinoid tumours') and cytotoxic agents.

Although approved therapies exist for the treatment of patients with locally advanced or metastatic NETs, they each have limitations. Moreover, these currently available treatments for advanced NETs are not curative. Combined with the facts of an increasing incidence of NETs, high relative prevalence and a trend toward more advanced stage at diagnosis, there is a great need for effective treatment options to help improve clinical outcomes for patients.

Main clinical studies

The phase 3 pivotal studies SANET-ep and SANET-p were designed and conducted synchronously, each targeting a different population (patients with extrapancreatic and pancreatic NETs, respectively), although sharing most design features, including double-blinding, 2:1 randomisation, experimental and control (placebo) arms, primary (PFS) and secondary (OS, ORR, DCR, DoR, TTR) efficacy endpoints, possibility of crossover from placebo to surufatinib at progression, and determinations on when to stop treatment – even the major protocol amendments were identical and took place at the same time. The main difference between the trials was the targeted population, since SANET-ep recruited patients with NETs of extrapancreatic origin (e.g. small intestinal, lung, etc.), while SANET-p only permitted pancreatic NETs.

Favourable effects

- **SANET-ep:** With 198 subjects randomised (129 surufatinib, 69 placebo) and 128 PFS events at data cut-off date (31-MAR-2019), the primary endpoint was met: a statistically significant improvement in INV-assessed PFS was seen when comparing the surufatinib arm (mPFS 9.2 months; 95% CI 7.4, 11.1) with the placebo arm (mPFS 3.8 months; 95% CI 3.7, 5.7), for a stratified HR of 0.33 (95% CI 0.22, 0.50) and p-value <0.0001. Regarding OS, an updated analysis with data cut-off on 30-OCT-2020 portraits 38% of OS maturity (82 deaths out of N=218) and shows mOS of 38.7 months (95% CI: 29.7, NE) in the surufatinib arm and 40.4 months (95% CI: 29.1, NE) in the placebo arm, for an estimated HR of 1.143 (95% CI 0.71, 1.85).
- **SANET-p:** With 172 subjects randomised (113 surufatinib, 59 placebo) and 95 PFS events at data cut-off date (11-NOV-2019), this trial also met its primary endpoint and declared a statistically significant improvement of INV-assessed PFS: mPFS of 10.9 months (95% CI 7.5, 13.8) in the surufatinib arm vs. 3.7 months (95% CI 2.8, 5.6) in the placebo arm, for a stratified HR of 0.49 (95% CI 0.32, 0.76) with a p-value 0.0011. Although still immature (26% of OS events, 46 out of N=179), the updated OS analysis, with data cut-off on 30-OCT-2020, does not indicate a potential detrimental effect of surufatinib vs. placebo: HR 0.85 (95% CI 0.46, 1.55).

Uncertainties and limitations about favourable effects

Overall efficacy results from both pivotal trials cannot be extrapolated to a European context: placebo was chosen as comparator in a clinical setting where diverse active treatments were already available at the time of design of the trials.

The recruited populations were too heterogenous (e.g. lines of treatment, staging, anatomic sites) and thus lack representativeness in a European setting. Baseline and response assessment diagnostic methods do not correspond to current clinical practice in EU, leading to uncertainties in patient selection and response assessment. Moreover, lack of access to local (e.g. liver-only disease) or systemic therapies (e.g. sunitinib, everolimus) was evident in both trials.

Change of assessment method –from BIIRC to investigator– of the primary endpoint while both pivotal studies were ongoing is not justified: clinical decisions for the patients were reliant on concurrent BIIRC. Considerable discrepancy exists between BIIRC and investigator assessed responses and the BIIRC-PFS results did not cross the efficacy boundary: the study would not have been positive at IA.

PFS results are immature and, hence, the estimated treatment effect not reliable: early unblinding of the study with immature data and the subsequent cross over of the placebo arm patients led to a situation where no further updates on PFS or OS would provide useful data.

Detrimental OS effect from surufatinib in SANET-ep study is not ruled out. Due to early stopping of the trial and early cross-over from the placebo arm, further analyses cannot address this concern.

In SANET-p, treatment-naïve patients (those treated as first line) experienced no efficacy benefit from surufatinib, contradicting usual treatment effects: better outcomes are expected in earlier lines of treatment.

Unfavourable effects

Nearly all patients in SANET-p/placebo (99.2%/96.7%) and SANET-ep/placebo (97.2%/95.2%) had at least one AE. In Analysis Set 2 it happened in 98.1% in the surufatinib treated patients. The most common AEs in Analysis Set 1 and 2, respectively was: proteinuria (68.8%/64.3%), hypertension (68.4%/54.7%), diarrhoea (49.0%/45.5%), bilirubin increased (37.6%/34.5%) and hypertriglyceridemia (35.7%/10.4%).

Notably 61.7% of the patients in the placebo arm had increased liver enzymes (AST or ALT), 19.5% had increased blood bilirubin and 54.9% had proteinuria which is considered unexpectedly high. As 1/3 of the population is treatment-naïve (potentially 1/3 of these treated in the placebo arm) the frequencies of AEs in the placebo arm of 22.6% having diarrhoea and abdominal pain, respectively is also considered high. However, the surufatinib treated patients had significantly more diarrhoea and abdominal pain (49% and 37.3%, respectively compared to 22.6% for both conditions in the placebo arm). The same was seen with constipation, asthenia and fatigue where it was seen in 13.7%, 16.3% and 14.1%, respectively compared to the placebo treated patients where it was seen in 4.5%, 8.3% and 4.1%, respectively.

The proportion of patients with Grade ≥3 AEs in the surufatinib treated patient groups was higher than in the placebo groups (74.9% vs 35.3%). The most common Grade ≥3 AEs were hypertension (38.8% vs 13.5%), proteinuria (14.8% vs 0.8%), hyperglyceridaemia (5.3% vs 0%) and anaemia (3.8% vs 3.0%) in the surufatinib treated patients compared to the placebo groups, respectively. These finding were consistent with the findings in Analysis Set 2.

SAEs were common during treatment (any grades 26.6% in Analysis Set 1 and 30.9% in Analysis Set 2) and most often related to gastrointestinal and hepatobiliary disorders (7.6% and 3.4% in Analysis Set 1 and 8.8% and 4.3%, respectively). The most common SAEs were high-grade events. The SAEs were generally small in numbers.

Seven (2.7%) patients with any TEAEs leading to death (Analysis Set 1) was seen in the surufatinib group vs 3 (2.3%) in the placebo group compared to 29 (4.0%) in Analysis Set 2.

Regarding clinically notable abnormality in ECG (QTc>480 msec) the incidence for the Analysis Set 2 was 3.8% and for Analysis Set 1 it was for surufatinib and placebo 6.1% vs 1.5%, respectively. For QTc prolonged >60 msec it was significantly higher for surufatinib compared to placebo (9.5% and 3.8%, respectively).

TEAEs leading to drug discontinuation occurred for 16.7% compared to 6.8% in the placebo group (17.7% for Analysis Set 2). By PT gastrointestinal disorders was the most frequent cause in 3.8% vs 1.5%, respectively (3.6% for Analysis Set 2).

Uncertainties and limitations about unfavourable effects

- The surufatinib treated patients seem to have a significantly worse QoL compared to patients in the placebo arm. As the placebo treated patients had an unexpectedly high frequency of AEs and seen in the light that a substantial number of these patients were treatment-naïve the difference in QoL between the 2 patient groups could be relatively even worse.
- There was a significantly prolonged QTc in the surufatinib treated patients and the MAH is requested to reflect the risk of QTc prolongation in section 4.8 of the SmPC, especially the increased risk with concomitant electrolyte abnormalities or medications with known risk of QTc prolongation.
- Surufatinib-induced hypertension does appear to be a potential risk factor for fatal CNS vascular disorder SAEs. In spite of the guidelines concerning prevention of high blood pressure, there were 6 patients (0,8%) with an SAE of CNS vascular disorder possibly related to surufatinib treatment.
- The evaluation of hemorrhages and the discussion of the Applicant reveals the fact that fatal gastrointestinal hemorrhages caused by surufatinib cannot be prevented by any guidelines in the SmPC given the nature of very short timelines for fatal hemorrhages.

Effects Table

Table 101. Effects Table for surufatinib (Total surufatinib treated subjects) (data cut-off:30 June 2020).

Effect	Short Description	Unit	Treatment Surufatinib	Control Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
SANET-ep INV-PFS	Investigator assessed progression free survival	months	9.2 (95% CI 7.4, 11.1)	3.8 (95% CI 3.7, 5.7)	Stratified HR-PFS 0.334 (95% CI 0.223, 0.499) P-value < 0.0001	CSR, SCE
SANET-ep OS	Overall survival	months	38.7 (95% CI 29.7, NE)	40.4 (95% CI 29.1, NE)	Stratified HR-OS 1.143 (95% CI 0.71, 1.85).	CSR, SCE
SANET-p INV-PFS	Investigator assessed progression free survival	months	10.9 (95% CI 7.5, 13.8)	3.7 (95% CI 2.8, 5.6)	Stratified HR-PFS 0.491 (95% CI 0.319, 0.755) P-value 0.0011	CSR, SCE
SANET-p OS	Overall survival	months	NE	NE	Stratified HR-OS 0.85 (95% CI 0.46, 1.55)	CSR, SCE
Unfavourable Effects						

Effect	Short Description	Unit	Treatment Surufatinib	Control Placebo	Uncertainties/ Strength of evidence	References
TEAEs of at least 10% in either treatment group	AE	%	98.1	96.2	NA	
≥Grade 3 AEs	AE(ADR)	%	74.9	35.3	NA	
SAEs	AE(ADR)	%	26.6	18.0	NA	
AEs leading to discont. of surufatinib	AE(ADR)	%	16.7	6.8	NA	
Proteinuria	ADR	%	68.8	54.9	NA	
Hypertension	ADR	%	68.4	27.1	NA	
Diarrhoea	ADR	%	49.0	22.6	NA	
Bilirubin increased	ADR	%	37.6	19.5	NA	
Hypertriglyceridaemia	ADR	%	35.7	12.0	NA	

Abbreviations: TEAE=Treatment-Emergent Adverse Event AE=Adverse Event SAE=Serious Adverse Event ADR=Drug related Adverse Event NA=Not Applicable NE=Not Evaluable

Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

NETs are rare tumours that arise from the diffuse neuroendocrine cells system and whose prognosis usually depends on location of the primary tumour, stage and degree of pathologic differentiation according to proliferation rate. Due to the complexity of the disease, systemic treatment regularly depends on the origin site of the tumour and other factors such as expression of serotonin receptors. For advanced disease, a plethora of therapeutic options has evolved in recent years, with systemic choices that highlight chemotherapy (especially for pNETs), selective serotonin analogs, everolimus, sunitinib and peptide receptor radionuclide therapy (e.g. ^{177}Lu-DOTATATE). Algorithms that adequate treatment according to anatomic origin of the tumour, histologic grade and other clinical factors exist since 2009 and were available at the time of design of pivotal trials SANET-ep and SANET-p, both of which started recruitment between 2015-2016.

Despite the apparent positive outcome of both pivotal trials supporting the efficacy of surufatinib in advanced NETs, a series of major objections was raised upon design and conduct of the pivotal studies, requesting explanations on changes in the primary endpoint, apparent detrimental OS effect in SANET-ep and diverse factors that jeopardise extrapolation (e.g. discrepant PFS between INV and BIIRC, low response rate, lack of support from results to unblind the study) of the data to a European context. The applicant provided a series of explanations, none of which satisfy the uncertainties posed, noting the lack of means to repair the decisions taken. Overall, efficacy of surufatinib for the intended indications is not considered established.

Regarding safety, however, comparison against placebo allowed for characterisation of the toxicity profile of surufatinib, noticing specific AEs with higher incidence in the experimental arm: hypertension, diarrhoea, abdominal pain, constipation, haemorraghes, fatigue and QTc prolongation. Since dose interruptions and reductions are feasible with oral administration, chances of tolerability improve. Nevertheless, it is noted that QoL was adversely affected in the surufatinib arm, not only because backbone symptomatic treatment with SSAs was not allowed, but because of important off-target toxicity. The risk of fatal CNS hemorrhages due to surufatinib-induced high blood pressure and the risk of fatal gastrointestinal hemorrhages caused by surufatinib remains and unavoidably highlights its unfavourable toxicity profile.

Balance of benefits and risks

Altogether, external validity of efficacy results is unavoidably compromised by the major objections, none of which were addressed appropriately with the responses provided.

Additional considerations on the benefit-risk balance

Not applicable.

Conclusions

The overall benefit /risk balance of surufatinib is negative due to several major objections.