Protocol #: LCI-GI-APX-NIN-001

TITLE: NINTEDANIB IN METASTATIC APPENDICEAL CARCINOMA

LAY TITLE: NINTEDANIB IN APPENDICEAL CANCER THAT HAS SPREAD

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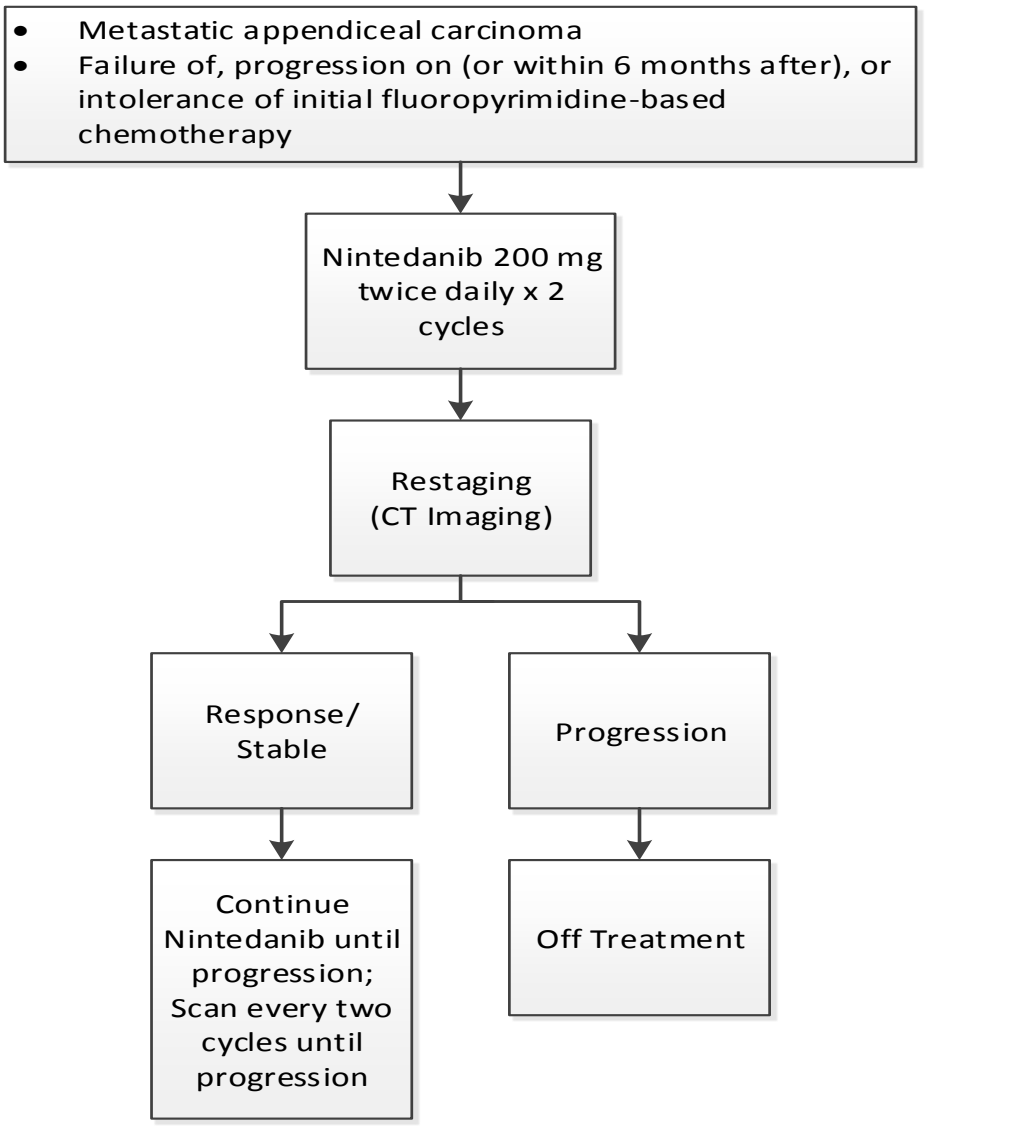
Investigational drug: Nintedanib

The study will be conducted in compliance with the protocol, ICH-GCP, and any applicable regulatory requirements.

Original Phase II / Version 3 / Dated 04/18/2018

PROTOCOL SUMMARY	
A. Study Title	Nintedanib in Metastatic Appendiceal Carcinoma
B. Indication	Metastatic appendiceal cancer after failure on fluoropyrimidine-based therapy
C. Clinical Phase	II
D. Summary of Rationale	Nintedanib is an oral tyrosine kinase inhibitor of VEGFR. It has demonstrated evidence of anticancer activity in lung and ovarian cancer in clinical trials, and is undergoing further investigation in metastatic colorectal cancer. Given the analogies between appendiceal and colorectal cancer and potentially ovarian cancer, and the limited information about the optimal treatment of metastatic appendiceal carcinomas, further investigation with nintedanib is warranted in this disease.
E. Study Objectives	The primary study objective is to evaluate the disease control rate. The secondary study objectives are to evaluate safety and toxicity, objective response rate, 6-month progression free survival and overall survival. Exploratory study objective include evaluation of serum VEGF, ascites VEGF, hypertension and paracentesis frequency in subjects with ascites at study entry.
F. Sample	Up to 39 subjects. Stage I: 28 evaluable subjects. If the study continues to Stage II: an additional 11 evaluable subjects
G. Inclusion Criteria	• Histologically confirmed stage IV appendiceal carcinoma • Failure of initial fluroropyrimdine-based chemotherapy. Failure is defined as progression on or within 6 months of therapy or intolerance of initial fluroropyrimdine-based chemotherapy • ECOG performance status score 0-2 • Measurable and/or evaluable, non-measurable disease according to RECIST 1.1 criteria
H. Dosage/ Dosage Form, Route, And Dose Regimen	Subjects will take oral nintedanib (200mg) twice daily. Dose reductions to 150mg and then 100mg twice daily as needed based on toxicity. Each cycle is 28 days.
I. Statistical Analysis	Disease control will be determined for each subject as a binary variable indicating whether or not the subject achieved a best overall response of CR, PR, or SD as determined by RECIST 1.1. Disease control rate will be estimated with the corresponding 95% Clopper-Pearson confidence interval. Objective response rate and 6-month PFS rate will be estimated with the corresponding 95% Clopper-Pearson confidence interval. Progression-free survival and overall survival rates will be estimated using Kaplan-Meier techniques. Multivariable regression models will be used to evaluate the impact of baseline subject and disease characteristics on outcomes. Incident rates for adverse events, SAEs, and deaths while on study therapy will be summarized.

SCHEMA



Endpoints
Primary: DCR
Secondary: OS, ORR, overall and 6 month PFS, safety/toxicity
Exploratory: Serum VEGF, hypertension, ascites VEGF, paracentesis

Statistical Plan
Single arm, two-stage design of 39 patients

LIST OF ABBREVIATIONS

β-HCG	β-human chorionic gonadotropin
γ-GT	γ-Glutamyl Transferase
5-HT_3	5-Hydroxy-Tryptamin receptor 3
AE	Adverse event
AESI	Adverse event of special interest
ALKP	Alkaline phosphatase
ALT / ALT (SGPT)	Alanine aminotransferase / Alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	Absolute neutrophil count
AP	Alkaline Phosphatase
AST / AST (SGOT)	Aspartate aminotransferase / Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
ATP	Adenosine triphosphate
bFGF	Basic fibroblast growth factor
BI	Boehringer Ingelheim
BID	Twice daily
BSA	Body surface area
BUN	Blood urea nitrogen
CHS	Carolinas HealthCare System
CI	Confidence interval
CK	Creatine kinase
CK-MB	Creatine kinase-MB
C_{max}	Maximum measured concentration of the analyte in plasma
CR	Complete response
CRC	Colorectal cancer
CRF/eCRF	Case report form / electronic case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical trial management system
DBP	Diastolic blood pressure
DILI	Drug-induced liver injury
DLT	Dose limiting toxicity
DSMC	Data Safety Monitoring Committee
DNA	Desoxyribo nucleic acid
ECG	Electro cardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FGR	Fibroblast growth factor
GCP	Good Clinical Practice

G-CSF	Granulocyte Colony Stimulating Factor
GI	gastrointestinal
GGTP	Gamma-glutamyltranspeptidase
GMP	Good Manufacturing Practice
HCC	Hepatocelluar carcinoma
HR	Hazard ratio
ICH	International Conference on Harmonisation
IB	Investigator brochure
ID	Identification
IDS	Investigational Drug Service
IIS	Investigator initiated study
INR	International normalized ratio
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
L	Litre
LCI	Levine Cancer Institute
LDH	Lactate dehydrogenase
LTF	Lost to follow-up
Lck	Lymphocyte-specific protein-tyrosine kinase, member of the Src family of kinases
Lyn	Yamaguchi sarcoma viral (v-yes-1) oncogene homolog, cellular protein tyrosine kinase member of the Src family of kinases
mg	Milligram
mCRC	Metastatic colorectal cancer
min	Minute
ml/mL	Millilitre
mm	Millimetre
MRI	Magnetic resonance imaging
MTOR	Mechanistic target of rapamycin
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OS	Overall survival
PD	Progressive disease
PDGF	Platelet derived growth factor
PDGFR	Platelet derived growth factor receptor
PFS	Progression free survival
P-GP	P-glycoprotein
PK	Pharmacokinetic(s)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
RAH	Research and Academic Headquarters
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual effect period
RET	Ret proto-oncogene

RCC	Renal cell carcinoma
RP2D	Recommended Phase 2 Dose
s	Second
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Stable disease
SOP	Standard operating procedure
Src	Src tyrosine kinase
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

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1. OBJECTIVES

1.1. Primary Objective

The primary study objective is to evaluate the disease control rate of nintedanib in subjects with Stage IV appendiceal carcinoma versus an inferred clinical historical disease control rate in the second line setting of 30%.
Disease control consists of subjects with measurable disease achieving complete response, partial response, or stable disease (as defined by RECIST 1.1[1]) and subjects with non-measurable disease with at least one disease assessment indicating non-progressive disease.

1.2. Secondary Objectives

The secondary study objectives are to evaluate:

- Safety and toxicity,
- Objective response rate,
- Overall and 6-month progression free survival, and
- Overall survival

1.3. Exploratory Objectives

Exploratory study objectives include:

- Evaluation of serum VEGF,
- Evaluation of ascites VEGF,
- Hypertension
- Frequency of paracentesis in subjects with ascites at study entry

2. BACKGROUND AND RATIONALE

2.1. Background

Appendiceal carcinomas are rare malignancies. This spectrum of malignant diseases is characterized by varying components of mucin production. The differential amounts of mucin that is present in the tumor appear to inversely correspond to aggressiveness of the malignancy. A frequent occurrence in metastatic appendiceal carcinomas is peritoneal carcinomatosis and/or malignant ascites or mucin production, leading to frequent parallels with ovarian and primary peritoneal cancer[2].

There are limited data regarding the efficacy of systemic therapy in the treatment of metastatic appendiceal carcinomas, and most of what has been presented is

retrospective in nature with its attendant limitations, such as patient selection and publication bias. Generally, patients have received therapy similar to a standard regimen for metastatic colorectal cancer, such as 5-fluorouracil, and leucovorin with or without oxaliplatin or irinotecan, and with or without the addition of monoclonal antibiodies such as bevacuzimab[3]. What has been published suggests that the response to chemotherapy, at least in the first line setting, is similar to standard chemotherapy. After an extensive review of the literature, we were unable to identify any data, beyond case reports, demonstrating consistent activity for any therapy in the second line setting in appendiceal carcinoma.

Over the past decade, there has been an increasing focus on the development of therapies that target specific molecular pathways. Although appendiceal carcinomas are relatively uncommon, there have been several reports suggesting that there are several potentially druggable targets worthy of further investigation[4]. For example, high vascular endothelial growth factor receptor (VEGFR)2 expression in appendiceal cancer has been correlated with poor survival[5]. Similarly, mammalian target of rapamycin (mTOR) has been correlated with a poorer progression free survival[6]. Since one downstream impact of mTOR is on angiogenesis, it appears that one common pathway in the development and progression of appendiceal cancer may be through the VEGF pathway and angiogenesis. Moreover, malignant ascites has been demonstrated to have elevated levels of VEGF[7]. In addition, in ovarian cancers, in which peritoneal metastases and malignant ascites are frequent, anti-VEGF therapy with VEGF targeting therapy including monoclonal antibodies like aflibercept, has been demonstrated to decrease the ascites, and can induce objective responses[8].

Angiogenesis is involved in tumour growth and development of metastases. Tumors induce blood vessel growth (angiogenesis) by secreting various growth factors (e.g. VEGF and bFGF). Vascular Endothelial Growth Factor (VEGF) and its high affinity receptor VEGFR-2 are crucial for the formation of new tumour vessels. In addition, there is preclinical evidence that fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) and their associated receptor tyrosine kinases substantially contribute to tumour angiogenesis. The VEGF - VEGFR-2 axis, besides promoting angiogenesis, may also be involved in stimulating growth of tumour cells themselves via an autocrine growth factor loop. This is suggested by in vitro data and immunohistochemical studies, e.g. for non-small cell lung cancer, ovarian carcinoma, gastric carcinoma, and malignant mesothelioma. Therefore, suppression of neoangiogenesis via inhibition of VEGFR-2 is a promising strategy for the treatment of human solid cancers. A substantial number of clinical trials with various inhibitors of VEGF or VEGFRs in various types of malignant tumors demonstrated this approach can convey clinical benefit, as monotherapy in RCC and HCC as well as in

combination therapy with standard chemotherapeutic drugs in NSCLC, CRC, Ovarian Cancer and others.

2.2. Experience with Nintedanib

2.2.1. Preclinical development and pharmacokinetics

Nintedanib is a potent, orally available triple kinase inhibitor targeting VEGFRs, PDGFRs, and FGFRs.

Nintedanib inhibits the signalling cascade mediating angiogenesis by binding to the adenosine triphosphate (ATP) binding pocket of the receptor kinase domain, thus interfering with cross-activation via auto-phosphorylation of the receptor homodimers.

The specific and simultaneous abrogation of these pathways results in effective growth inhibition of both endothelial and, via PDGF- and FGF-receptors of perivascular cells which may be more effective than inhibition of endothelial cell growth via the VEGF pathway alone. Furthermore, signalling by FGF-receptors has been identified as a possible escape mechanism for tumour angiogenesis when the VEGF pathway is disrupted.

Besides inhibition of neo-angiogenesis, it may alter tumour maintenance by inducing apoptosis of tumour blood vessel endothelial cells. Inhibition of receptor kinases may also interfere with autocrine and paracrine stimulation of tumour angiogenesis via activation loops involving VEGF, PDGF, and bFGF utilized by vascular and perivascular cells such as pericytes and vascular smooth muscle cells.

In addition, preclinical models show that nintedanib may have a direct anti-tumour effect on those malignant cells which overexpress PDGFR and/or FGFR (e.g. H1703 NSCLC cells).

	IC_{50} (nmol/L)
VEGFR (1 / 2 / 3)	34 / 21 / 13
PDGFR (α / β)	59 / 65
FGFR (1 / 2 / 3)	69 / 37 / 108
Flt-3	26
RET	35
Src, Lck, Lyn	156 / 16 / 195

In vitro, the target receptors are all inhibited by nintedanib in low nanomolar concentrations. In in vivo nude mouse models, nintedanib showed good anti-tumour efficacy at doses of 50 – 100 mg/kg, leading to a substantial delay of tumour growth or even complete tumour-stasis in xenografts of a broad range of differing human tumour types. Histological examination of treated tumors showed a marked reduction of tumour vessel density by approximately 80%[9].

The metabolism of nintedanib was predominantly characterized by the ester cleavage of the methyl ester moiety yielding BIBF 1202, which was further metabolized by conjugation to glucuronic acid yielding the 1-O-acylglucuronide. Data collected in this study show that nintedanib has a favorable PK and excretion profile with almost no elimination via the urine, only 0.7% of total [14C] radioactivity was eliminated via the urine[10]. The metabolic characteristics are predominantly independent of cytochrome P450-catalysed metabolic pathways[11].

A soft gelatine capsule formulation of nintedanib is used in humans. After oral administration, nintedanib is absorbed quickly. Maximum plasma concentrations (Cmax) generally occur 2 to 4 hours after administration. So far, no evidence for a deviation from dose proportionality of the PK of nintedanib has been observed. Steady state is reached latest after one week of dosing. The terminal half-life of nintedanib is in the range of 7 to 19 h. Nintedanib is mainly eliminated via feces[11].

Nintedanib is non-mutagenic, even at high doses.

Two exploratory studies in rats revealed a teratogenic effect of nintedanib with a steep dose/effect relationship and an early onset of embryo fetal deaths at low dosages. This effect was observed at dose levels resulting in plasma drug concentrations comparable to or below those in humans. Because the concentration of nintedanib in semen is unknown, males receiving nintedanib and having sexual intercourse with females of childbearing potential should use latex condoms. Women of childbearing potential should be advised to use adequate contraception during and at least 3 months after the last dose of nintedanib.

2.2.2. Clinical development of nintedanib

Nintedanib is being evaluated in several cancers. Additionally, nintedanib is in advanced phase III for the non-cancer indication idiopathic pulmonary fibrosis (IPF). As of 15 Feb 2013, 3556 cancer patients, over 1000 patients with IPF, and 140 healthy volunteers had been treated with nintedanib or nintedanib matching placebo, in monotherapy or in combination with chemotherapy.

Phase I

Phase I dose selection studies revealed that nintedanib is generally well tolerated with mild to moderate adverse effects such as gastrointestinal symptoms (nausea, diarrhea, vomiting, abdominal pain) and reversible elevations of liver enzymes. Initial signs of clinical activity including an encouraging rate of patients with stabilisation of their tumour of 54% and 68%, respectively, have been observed in patients with various solid tumors[12].

Based on the Phase I dose escalation trials with nintedanib monotherapy, the maximum tolerated dose was defined to be 250 mg for twice daily dosing in Caucasians and 200 mg twice daily in Japanese patients with a manageable safety profile in advanced cancer patients. Based on the overall safety profile, the RP2D for nintedanib as monotherapy is 200 mg bid.

The maximum tolerated dose for combination therapy of nintedanib in combination with pemetrexed, docetaxel, paclitaxel/carboplatin and FOLFOX is 200mg bid. Combination of nintedanib with other anti-cancer drugs revealed a similar adverse event profile as compared to nintedanib monotherapy except for the chemotherapy related toxicities. There was no change of the pharmacokinetic parameters of nintedanib or of the cytotoxic compounds due to the combined treatment. Dose limiting toxicity consisted mostly of liver transaminase elevations as in the monotherapy phase I trials with the exception of the combination of nintedanib with pemetrexed, where fatigue was the most relevant dose limiting toxicity.

Available pharmacokinetic data indicate that the systemic exposure needed for biological activity can be achieved starting with doses of 100 mg nintedanib once daily.

The predominant adverse events were nausea, diarrhea, vomiting, abdominal pain and fatigue of mostly low to moderate severity. Dose limiting toxicities (DLT) were mainly confined to reversible hepatic enzyme elevations (AST, ALT, γ-GT) which increased dose-dependently. Most cases occurring at doses of 250 mg and above, and a very low incidence at doses below 200 mg and were reversible after discontinuation of nintedanib treatment. All adverse events observed after single administration of single doses of nintedanib to healthy volunteers were only of CTCAE grade 1 severity and fully reversible[11].

NSCLC

In a phase II trial in NSCLC patients the safety profile of nintedanib observed in phase I trials could be confirmed. Most commonly reported drug-related AEs were

nausea (57.5%), diarrhea (47.9%), vomiting (42.5%), anorexia (28.8%), abdominal pain (13.7%) and reversible alanine transaminase (13.7%) and aspartate aminotransferase elevations (9.6%) In conclusion it was generally well tolerated and displayed single agent activity in advanced or recurrent NSCLC patients. Median overall survival (OS) was 21.9 weeks. Eastern Cooperative Oncology Group (ECOG) 0–1 patients (n = 56) had a median PFS of 11.6 weeks and a median OS of 37.7 weeks. Tumour stabilisation was achieved in 46% of patients (ECOG 0–1 patients: 59%), with one confirmed partial response (250 mg bid.)[13].

LUME-Lung 1 was an international, randomized, double-blind, phase III trial assessing the efficacy and safety of docetaxel plus nintedanib as second line therapy for non-small-cell lung cancer (NSCLC). In total, 1314 patients with Stage IIIB/IV or recurrent NSCLC (all histologies) who had progressed after 1st line chemotherapy were randomized in 1:1 fashion to either receive Nintedanib 200mg BID + Docetaxel (n=655) or Placebo BID + Docetaxel (n=659).

LUME-Lung 1 met its primary endpoint by showing a statistically significant improvement of PFS for all patients regardless of histology (median PFS 3.4 versus 2.7 months; HR 0.79, p=0.0019) for nintedanib in combination with docetaxel[10].

A significant improvement in OS was demonstrated in patients with adenocarcinoma; median OS 12.6 months [95% CI 10·6–15·1] vs 10·3 [95% CI 8·6 –12·2] months; HR 0·83 [95% CI 0·70 –0·99], p=0·0359); the Kaplan -Meier survival curves separate at 6 months, continuing throughout the 36-month study observation period. One year overall survival was 52·7% (95% CI 46·8 –57·9) in the docetaxel plus nintedanib group compared with 44·7% (38·9 –49·8) in the docetaxel plus placebo group; 2 year overall survival was 25·7% (95% CI 20·5 –30·2) in the docetaxel plus nintedanib group compared with 19·1% (14·4 –23·2) in the docetaxel plus placebo group[10].

In the predefined population of patients with adenocarcinoma who had progressed within 9 months after start of first-line therapy, overall survival was significantly longer in the docetaxel plus nintedanib group than in the docetaxel plus placebo group (median overall survival 10·9 months [95% CI 8·5–12·6] vs 7·9 months [6·7 – 9·1]; HR 0·75 [95% CI 0·60 –0·92], p=0·0073)[10].

In the total population of patients (all histologies), there was no difference in overall survival between the two groups: median overall survival was 10·1 months (95% CI 8·8–11·2) in the docetaxel plus nintedanib group compared with 9·1 (8·4 –10·4) months in the docetaxel plus placebo group (HR 0·94 [95% CI 0·83 –1·05], p=0·2720)[10].

Nintedanib plus docetaxel had a manageable safety profile with no unexpected safety findings. The predominant adverse events were nausea, diarrhea, vomiting, abdominal pain and fatigue of mostly low to moderate intensity after monotherapy with nintedanib. Adverse events that were more common (≥5% difference) in the docetaxel plus nintedanib group than the docetaxel plus placebo group were: diarrhea (all grades, 276 of 652 [42·3%] vs 143 of 655 patients [21·8%]; grade ≥3, 43 [6·6%] vs 17 [2·6%]), increases in alanine aminotransferase (all grades, 186 [28·5%] vs 55 [8·4%]; grade ≥3, 51 [7·8%] vs six [0·9%]), nausea (all grades, 158 [24·2%] vs 118 [18·0%]; grade ≥3, five [0·8%] vs six [0·9%]), increases in aspartate aminotransferase (all grades, 147 [22·5%] vs 43 [6·6%]; grade ≥3, 22 [3·4%] vs three [0·5%]), decreased appetite (all grades, 145 [22·2%] vs 102 [15·6%]; grade ≥3, nine [1·4%] vs eight [1·2%]), and vomiting (all grades, 110 [16·9%] vs 61 [9·3%]; grade ≥3, five [0·8%] vs three [0·5%];). Most of these adverse events were manageable with supportive treatment or dose reduction[10].

LUME-Lung 2 was a similar randomised, double-blind, phase III study of nintedanib plus pemetrexed versus placebo plus pemetrexed in patients with advanced non-squamous non-small cell lung cancer after failure of first line chemotherapy[14].

Based on a pre-planned futility analysis of investigator-assessed PFS, enrolment was halted after 713/1300 planned patients had been enrolled. The analysis (based on conditional power for PFS by investigator assessment) suggested that the study was futile and that the primary endpoint of centrally assessed PFS would likely not be met. The futility analysis was based on conditional power; there was no formal testing of null hypothesis as planned for primary analysis no safety issues were identified.

Even though the study was stopped prematurely, the primary endpoint of this Phase III trial was met; treatment with nintedanib plus pemetrexed resulted in a significant prolongation of centrally reviewed PFS compared with placebo plus pemetrexed (median PFS 4.4 vs. 3.6 months with a HR 0.83; p=0.0435). The disease control rate was also increased significantly in nintedanib-treated patients. There was no improvement in OS in nintedanib-treated patients. Nintedanib 200 mg bid in combination with pemetrexed had an acceptable and manageable safety profile, with no new or unexpected safety findings. The most frequent AEs were reversible increases in liver enzymes and gastrointestinal events[14].

Ovarian Cancer

A randomised phase II maintenance trial in ovarian cancer in which the efficacy and safety of nine months of continuous twice daily doses of nintedanib following chemotherapy was investigated, has identified the potential activity of nintedanib

with a 36-week PFS of 16.3 % compared to 5.0 % in the control group. The safety profile was consistent with findings previously reported for nintedanib administered as monotherapy as mentioned above[15].

Nintedanib was evaluated in a Phase III randomized, placebo-controlled, double-blind, multicentre ovarian study with 1366 patients. Patients received nintedanib plus paclitaxel and carboplatin or placebo plus paclitaxel and carboplatin for six cycles. This was followed by monotherapy nintedanib or placebo for up to 120 weeks. The trial met its primary endpoint by demonstrating a statistically significant improvement in progression-free survival (HR 0.84; 95%CI 0.72 - 0.98; p=0.0239, median PFS 17.3 months for nintedanib and 16.6 months for placebo). The trial remains blinded for OS as the data were immature at the time of the primary analysis. Main adverse events were GI side effects and increased hematological toxicity[16].

Colorectal Cancer
A Phase I/II, open-label, randomised study of nintedanib plus mFOLFOX6 compared to bevacizumab plus mFOLFOX6 in 120 patients with metastatic colorectal cancer was performed, demonstrating an acceptable safety profile of nintedanib in combination with mFOLFOX 6. In comparison to bevacizumab, nintedanib showed a similar magnitude of efficacy, a similar safety/tolerability profile, a similar exposure and dose intensity of mFOLFOX6[17].

A Phase III study was completed after recruiting more than 760 participants worldwide to evaluate the efficacy of nintedanib in patients with metastatic colorectal cancer (mCRC) after failure of previous treatment with standard chemotherapy and biological agents (ClinicalTrials.gov Identifier: NCT02149108).

Renal Cell Cancer
Nintedanib has been studied in a randomized phase II study in metastatic clear cell RCC with sunitinib as the control arm. Similar efficacy was seen in both arms of this study. AEs observed more frequent in the nintedanib arm included diarrheal, nausea, fatigue and infection, whereas AEs more frequent in the sunitinib arm consisted of bleeding, anaemia, hypertension, hand-foot syndrome and stomatitis.

Hepatocellular Cancer
The efficacy and safety of nintedanib versus sorafenib in Asian patients with advanced hepatocellular carcinoma was investigated in a randomised phase II trial. Nintedanib showed similar efficacy to sorafenib, with a favourable and manageable AE profile. More patients in the sorafenib arm had severe AEs and drug-related AEs compared with patients in the nintedanib arm, and more patients in the sorafenib arm

required dose reduction compared with the nintedanib arm. Nintedanib AEs were manageable; in the nintedanib arm there were fewer hypertension, palmar-plantar erythrodysaesthesia syndrome, and transaminase elevation events[18].

For more details please refer to the investigator drug brochure for nintedanib.

2.3. Study/Dose Rationale

2.3.1. Study Rationale

Nintedanib (BIBF 1120) is an oral tyrosine kinase inhibitor of VEGFR. It has demonstrated evidence of anticancer activity in lung and ovarian cancer in clinical trials, and is undergoing further investigation in metastatic colorectal cancer. Given the analogies between appendiceal and colorectal cancer and potentially ovarian cancer, and the limited information about the optimal treatment of metastatic appendiceal carcinomas, further investigation with nintedanib is warranted in this disease.

2.3.2. Dose Rationale

The dose of nintedanib was selected based on doses evaluated in single agent and combination studies in patients with cancer, or others with idiopathic fibrosis. The most extensive experience with nintedanib in patients with malignancy is in lung cancer. Nintedanib was evaluated at 150 mg twice daily and 250 mg twice daily in patients with stage IIIB and IV non-small cell lung cancer (NSCLC) after first or second line platinum based chemotherapy in a randomized phase II study. They reported no clear difference in efficacy, though the only confirmed partial response was at the 250 mg BID dose. It did appear that patients receiving the higher dose did experience more frequent grade 3-4 elevations in transaminases and GGTP, diarrhea and nausea. Interestingly, no grade 3 or 4 hypertension was reported[13]. Thus, a phase 3, double-blind, placebo-controlled study was performed in 1314 patients with NSCLC in the second line setting, comparing docetaxel with 200 mg po BID of nintedanib with docetaxel and placebo. This study demonstrated that the addition of nintedanib to docetaxel significantly improved the median progression free survival, compared to docetaxel and placebo (3.5 months, compared to 2.7 months), meeting the study's primary endpoint. Even in combination with docetaxel, nintedanib was fairly well tolerated, with the most common severe toxicities again being diarrhea, and transaminase elevations[10]. In two large randomized, double-blind phase 3 studies totaling 1066 patients with idiopathic pulmonary fibrosis, nintedanib 150 mg twice daily was compared to placebo, and proved to be well tolerated, with the most common toxicities being diarrhea and elevations in the liver enzymes, but less than 5%

of patients discontinued nintedanib because of toxicities. However, it should be noted that five patients (1.6%) had a myocardial infarction while on nintedanib, compared to one (0.5%) who was treated with placebo[19]. Taken together, this data suggests that nintedanib at doses from 150 to 200 mg, and perhaps 250 mg twice daily is tolerable, and should be investigated at a dose of 200 mg twice daily as a single agent in the second line setting.

3. BENEFIT/RISK ASSESSMENT

Although considerable progress has occurred in understanding the biological characteristics of cancer as well as the development of more effective treatment regimens, most patients with locally advanced or metastatic tumors succumb to their disease. Thus, there is a substantial need for novel therapeutic strategies to improve the outcome for patients with advanced or metastatic appendiceal carcinoma.

Antiangiogenic treatment with the orally available triple angiokinase inhibitor nintedanib with inhibition of VEGFR, PDGFR and FGFR offers the chance to control both locally recurrent and distant metastatic disease on an outpatient basis. Treatment with nintedanib may have the potential to provide significant benefit to patients with locally advanced and/or metastatic appendiceal carcinoma by slowing tumor progression and metastasis, since its cellular target is expressed on the tutor vasculature in most malignancies. Induction of endothelial cell apoptosis may result in subsequent degradation of tumor vessels and subsequent tumor necrosis. Additionally tumor growth may be affected by direct anti-tumor effects, e.g. tumor cells that express VEGFR, PDGFR, or FGFR.

The main risks of therapy with nintedanib in adult patients are:

- the gastro-intestinal AEs (diarrhea nausea, vomiting, abdominal pain)
- increases in liver enzymes (AST, ALT, ALKP) and bilirubin
- Perforation (gastrointestinal and non-gastrointestinal)
- Hypertension
- Venous thromboembolism
- Bleeding
- Neutropenia and sepsis, if combined with myelosuppressive chemotherapy
- Pancreatitis

Liver enzymes must be followed closely during treatment with nintedanib.

Therapy with the trial drug must be interrupted in the event of relevant elevations of liver enzymes and/or of bilirubin and further treatment is to be withheld until recovery of the abnormal laboratory parameters.

Hypertension is a side effect of nintedanib and a slightly increased frequency of hypertension has been observed in the trials with nintedanib to a mild to moderate degree and only few cases of CTCAE grade 3 or 4 hypertension have been observed. With respect to bleeding, in the LUME –Lung 1 trial involving 1314 patients more bleeding events were reported for nintedanib-treated squamous cell carcinoma patients (all grades: 17.1% vs. 10.9%; grade ≥3: 2.9% vs. 1.3%) than for those with adenocarcinoma (all grades: 10.9% vs. 11.1%; grade ≥3: 1.5% vs. 1.3%). Fatal bleeding events were balanced between both arms regardless of histology.

Based upon a non-clinical safety study *in vitro*, nintedanib may have a potential risk of phototoxicity (skin and eyes) *in vivo*. Few cases of photosensitivity reactions (less than 1 %) and of CTCAE grade 1 intensity only have been reported from the clinical studies to date. If adequate precautions are taken (avoidance of prolonged ultraviolet exposure, use of broad spectrum sunscreen and sunglasses), treatment with nintedanib is considered safe.

4. SUBJECT SELECTION

4.1. Accrual

This study will enroll up to 39 subjects in 2 stages with appendiceal carcinoma that have failed (defined as progression on or within 6 months or intolerance of) initial fluoropyrimidine-based chemotherapy. It is anticipated the duration of accrual will be 48 months. Both men and women of all races and ethnic groups are eligible for this trial.

4.2. Eligibility Criteria

4.2.1. Inclusion Criteria

Subjects must meet <u>all</u> of the following criteria:

a. Age ≥ 18 years old

b. Histologically confirmed appendiceal carcinoma stage IV

c. Failure of initial fluoropyrimidine -based chemotherapy. Failure is defined as progression on or within 6 months of last day of therapy or intolerance of initial fluroropyrimdine-based chemotherapy.

d. Life expectancy at least 3 months

e. ECOG performance status score 0-2

f. Presence of measurable and/or evaluable, non-measurable disease according to RECIST 1.1 criteria

g. Written informed consent signed and dated by subject or Legally Authorized Representative (LAR) prior to admission to the study in accordance with ICH-GCP guidelines and to the local legislation.

4.2.2 Exclusion Criteria

Subjects must not meet any of the following criteria.

a. Prior treatment with nintedanib or any other VEGFR inhibitor

b. Known hypersensitivity to peanut or soya or to contrast media. History of hypersensitivity to contrast media is allowed if the subject is able to tolerate contrast media with pre-medication.

c. Chemo-, hormone-, radio-(except for brain and extremities) or immunotherapy or therapy with monoclonal antibodies or small tyrosine kinase inhibitors withinthe past 4 weeks prior to treatment with the trial drug.

d. Radiotherapy to any target lesion within the past 3 months prior to baseline imaging when that target lesion is the only target lesion identified on baseline imaging, unless it has subsequently grown.

e. Persistence of clinically relevant therapy related toxicity from previous chemo and/or radiotherapy as determined by the investigator.

f. Active brain metastases (e.g. stable for <4 weeks, no adequate previous treatment with radiotherapy, symptomatic, requiring treatment with anti-convulsants; dexamethasone therapy will be allowed if administered as stable dose for at least one month) or leptomeningeal disease.

g. Radiographic evidence of cavitary or necrotic tumors.

h. Tumors with radiographic evidence (CT or MRI) of local invasion of major blood vessels.

i. Anti-neoplastic treatment for appendiceal cancer, with other investigational drugs or treatment in another clinical trial within 30 days before start of study treatment.

j. Therapeutic anticoagulation with drugs requiring INR monitoring (except low-dose heparin and/or heparin flush as needed for maintenance of an in-dwelling intravenous devise) or anti-platelet therapy (except for low-dose therapy with acetylsalicylic acid ≤ 325mg per day).

k. Major injuries and/or surgery within the past 4 weeks prior to start of study treatment, incomplete wound healing or planned surgery during the on-treatment study period.

l. History of clinically significant hemorrhagic or thromboembolic event in the past 6 months prior to consent.

m. Known inherited predisposition to bleeding or thrombosis.

n. Significant cardiovascular diseases (i.e. uncontrolled hypertension, unstable angina, history of infarction, congestive heart failure > NYHA II, serious cardiac arrhythmia, pericardial effusion) within the past 12 months prior to start of study treatment.

o. Proteinuria CTCAE grade 2 or greater.

p. Creatinine > 1.5x ULN or GFR < 45 ml/min.

q. Hepatic function: total bilirubin above normal limits; ALT or AST > 1.5x ULN in subjects without liver metastasis. For subjects with liver metastasis: total bilirubin above normal limits; ALT or AST > 2.5x ULN.

r. Coagulation parameters: International normalised ratio (INR) > 2x ULN, prothrombin time (PT) and partial thromboplastin time (PTT) ≥ 1.5x ULN.

s. Absolute neutrophil count (ANC) < 1500/ml, platelets < 100000/ml, Hemoglobin < 9.0 g/dl.

t. Other malignancies at the time of signing the informed consent other than basal cell skin cancer or carcinoma in situ of the cervix.

u. Active serious infections if requiring systemic antibiotic or antimicrobial therapy.

v. Active or chronic hepatitis C and/or B infection.

w. Gastrointestinal disorders (like chronic diarrhea) or abnormalities that would interfere with absorption of the study drug per investigator discretion. Subjects with this disorder may be allowed if able to tolerate anti-diarrheal medications like loperamide.

x. Serious illness or concomitant non-oncological disease such as neurologic, psychiatric, infectious disease or active ulcers (gastro-intestinal tract, skin) or laboratory abnormality that may increase the risk associated with study participation or study drug administration and in the judgment of the investigator would make the subject inappropriate for entry into the study.

y. Sexually active women of child-bearing potential and men who are sexually active with women of child-bearing potential and unwilling to use at least 2 medically acceptable method of contraception (e.g. such as implants,

injectables, combined oral contraceptives, some intrauterine devices or vasectomized partner for participating females, condoms for participating males) during the trial and for at least three months after end of active therapy. Female subjects will be considered of child-bearing potential unless surgically sterilized by hysterectomy or bilateral tubal/salpingectomy, or post-menopausal for at least 2 years.

z. Pregnancy or breast feeding; female participants of child-bearing potential must have a negative pregnancy test (β-HCG test in urine or serum) before commencing study treatment.

aa. Psychological, familial, sociological, or geographical factors potentially hampering compliance with the study protocol and follow-up schedule per the investigator.

bb. Alcohol or drug abuse which in the determination of the investigator would interfere with trial participation.

cc. Significant weight loss, (> 10% of baseline weight) within past 2 months prior to consenting for the trial. Removal of ascites should not be calculated as weight loss. For subjects who have had ascites removed within the 2 months prior to consent, the S-I should be consulted.

4.3. Reproductive Risks

Nintedanib can cause harm to developing fetus. For this reason, males and females of childbearing potential will be counseled on the need to use adequate contraception (eg, oral contraceptives, intrauterine devices, barrier methods) for all sexual encounters prior to start of study therapy and for at least 3 months following discontinuation of study therapy.

Female subjects will be considered to be of childbearing potential unless surgically sterilized by hysterectomy or bilateral tubal ligation/salpingectomy, or post-menopausal for at least two years.

Women of childbearing potential who are sexually active and not using at least 2 medically acceptable method of contraception (e.g. such as implants, injectables, combined oral contraceptives, some intrauterine devices or vasectomized partner for participating females) during the trial and for at least three months after the end of active therapy are not allowed to participate in the trial.

Men will also be counseled on the need to use contraception for all sexual encounters.

5. INVESTIGATIONAL PLAN

5.1. Study Milestones

Registration date: the date the subject signs informed consent.

Eligibility date: the date of the last documented criterion that confirmed subject eligibility.

Enrollment date: the date of initiation of nintedanib treatment.

Treatment discontinuation date: the date the Investigator decides to discontinue the subject from nintedanib treatment for any reason.

5.2. Overall Study Design

This is a single arm, two-stage phase II study designed to evaluate disease control rate in subjects with metastatic appendiceal carcinomas who have had failure of initial fluroropyrimdine-based chemotherapy.

In the first stage, a total of 28 subjects in the evaluable population will be enrolled. Of these, if at least 8 should achieve disease control (Section 13.1.1) the study will continue on to the second stage. In the second stage, 11 participants in the evaluable population (total of 39) will be enrolled. If at least 16 of the 39 total subjects enrolled achieve disease control, then we will be able to reject the null hypothesis. The sample size of evaluable population for both Stage 1 and Stage 2 include participants who begin nintedanib therapy.

Following informed consent and eligibility check, subjects will be enrolled and treated with 200mg of oral nintedanib two times per day and undergo disease evaluation after two months. Subjects who progress will be discontinued from study treatment and those who do not progress will continue twice daily treatment with nintedanib and will continue to undergo disease evaluation every two cycles.

Data from this study will be collected on electronic case report forms (eCRFs) and stored in the clinical trials management system (CTMS).

5.3. Informed Consent

Written informed consent will be obtained from each subject prior to undergoing protocol-specific evaluations or procedures and prior to receiving treatment. In addition, all subjects will provide authorization for the release of their medical records for research purposes.

5.4. Registration/Enrollment/Discontinuation

5.4.1. Subject Registration/Enrollment

Following informed consent, subjects will be registered by the Sponsor and assigned a Study ID number. The Study ID will be a four-digit number sequentially assigned, where 1001 will be the Study ID number assigned to the first registered subject. Following eligibility check per standard operating procedures, eligible subjects will be enrolled on the first date of nintedanib dosing. Study ID numbers assigned to registered subjects not ultimately enrolled will not be re-assigned.

5.4.2. Subject Withdrawal

Subjects are defined as withdrawn from the study if they revoke consent for both treatment and study procedures or the Investigator withdraws them from the study. Subjects **must be** withdrawn from the trial for any of the following reasons:

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at his/her own request. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Subject is lost to follow-up after three consecutive unsuccessful documented attempts at contacting the subject.
- Development of an intercurrent illness or situation which would, in the judgment of the Investigator, significantly affect assessments of clinical status and trial endpoints.

Subjects may be completely withdrawn from the study by the Investigator if criteria for long-term follow-up described in Section 5.5 are met.

Any subject who withdraws themselves or who is withdrawn from the study by the Investigator will remain under medical supervision until discharge or transfer is medically acceptable.

In all cases, the reason for withdrawal must be documented in the subject's medical records and/or research chart and recorded in the CTMS. Withdrawn subjects are considered to be off-study. Details for the premature termination of the study as a whole are provided in Section 14.2**.**

5.4.3. Screen Failures

A subject who, for any reason (i.e. failure to satisfy the eligibility criteria or withdraws consent), terminates his/her study participation before receiving first dose of study therapy is regarded as a "screen failure." All screen failures will be tracked in the CTMS.

5.5. Study Procedures

Demographics and Medical/Treatment History. Demographics and medical/treatment history will be collected during screening. Medical and treatment history (oncological and relevant non-oncological) will be collected. Cancer history and the following information (including but not limited to) will be obtained:

- Date of first histological/cytological diagnosis
- Prior cancer therapy

All significant medical history findings that occurred prior to the subject signing informed consent will be documented.

Pregnancy Test. A urine or serum pregnancy test will be performed at screening and as clinically indicated for women of childbearing potential.
Women who are pregnant and/or breast-feeding are ineligible for study participation.

Physical Examination. Physical exam by body system, height, weight, body surface area (BSA) and ECOG performance status will be documented during screening and Week 1 of each cycle per Section 6. Height to be assessed at screening only.

Vital Signs. Vital signs will be recorded at screening and Week 1 of each cycle per Section 6 and should include temperature, pulse rate, respiratory rate, blood pressure and oxygen saturation. Blood pressure (only) will be assessed on Day 8 and Day 15 (+/- 2 days) during the first 2 cycles of study treatment. Blood pressure assessment may be done at home by the subject or at another clinic (i.e. local pharmacy) and the

research staff will be responsible for obtaining these results from the subject. Phone contact is acceptable.

Adverse Event Evaluation. All adverse events and serious adverse events will be monitored and documented (regardless of grade or attribution) and reported on an ongoing basis per Section 11. Investigators should refer to the Safety Information section of the current IB for nintedanib. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions.

Concomitant Medications. All medication that is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the Investigator. All medications taken within 2 weeks prior to the enrollment date and during the study must be recorded.

Permitted concomitant therapies include:

- Standard therapies for concurrent medical conditions.
- Supportive care for any underlying illness.
- Palliative radiation therapy is allowed if the target lesion(s) are not included within the radiation field and no more than 10% of the bone marrow is irradiated.
- Granulocyte colony-stimulating factor (G-CSF) and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the Investigator's discretion. However, they may not be substituted for a required dose reduction. Subjects are permitted to take chronic erythropoietin.
- Treatment with nonconventional therapies (such as acupuncture), and vitamin/mineral supplements are permitted provided that they do not interfere with the study endpoints, in the opinion of the Investigator.
- Bisphosphonates.
- Subjects taking narrow therapeutic index medications should be monitored proactively (e.g. phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporine, and digoxin).

Laboratory Tests. The blood-based clinical laboratory tests at screening will include a complete blood count with differential and platelets, a comprehensive metabolic panel (including sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, and calcium, albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), total bilirubin, direct bilirubin only if total bilirubin is above normal, and total protein), PTT, PT/INR and urinalysis (UA). After enrollment, a complete blood count with

differential and platelets and a comprehensive metabolic panel (including sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), total bilirubin, direct bilirubin only if total bilirubin is above normal and total protein) will be performed according to the Study Calendar.

Correlative Studies. Ascites will be removed from the subject when required as a part of standard of care and the entire volume that is removed for clinical purposes and remaining after any diagnostic tests will be processed to concentrate any cells and create a cell block(s) by CHS Pathology. The ascites cell block will be banked and stored at room temperature at the BSR for VEGF levels and for future assays.

Serum (2- 10 ml tubes) specimens from subjects and will be processed within one hour of collection, if possible, but may be kept at 4°C for no longer than 4 hours before processing. Serum will be processed and stored at -80°C until future testing. Specimens will be stored at the CHS Biospecimen Repository.

Specimens will be collected according to the schedule in Section 6. Specimens will be collected after subject eligibility confirmation, but prior to administration of the first dose of nintedanib and subsequent cycles. Exploratory biomarker arrays may be used.

Radiology and Tumor Measurements. A computed tomography (CT) scan with oral and intravenous contrast of the chest, abdomen and pelvis will be performed within 28 days prior to the first dose of nintedanib (screening scan). Scans will then be performed within 7 days following anticipated completion of cycle 2 unless clinically proven otherwise and within 7 days of anticipated completion of every two cycles thereafter (e.g. end of cycles 4, 6). A contrast-enhanced MRI of the abdomen and pelvis and a CT scan of the chest without contrast may be substituted if clinically necessary; however, subsequent studies must be performed using the same imaging modality throughout the study period.

For subjects who discontinue study therapy due to toxicity or reasons other than progressive disease, every effort will be made to obtain imaging studies and tumor assessments every 8 weeks (+/- 2 weeks) until documented progression or the start of subsequent anti-cancer therapy.

Subsequent Therapy and Survival Status. Once subjects complete their End of Treatment visit, they will be followed until all treatment-related toxicities have resolved, returned to baseline, stabilized, or are deemed irreversible. Subject's initial anti-cancer therapy following discontinuation of nintedanib treatment and survival

status will be documented.

Subjects (or their family members or designees) may be contacted by telephone, in writing, or during clinic visits after treatment discontinuation for collection of long-term follow-up data approximately every 6 months until death or lost to follow-up, or until the criteria defined for the final analysis (Section 13.3.1) are reached. However, in the event the criteria for the final analysis are met, and there are subjects who have not yet been discontinued from nintedanib treatment, subjects in follow up will continue to be followed until all subjects have discontinued study treatment and completed the safety monitoring period. Long-term follow-up clinical information may also be obtained through chart reviews.

6. STUDY CALENDAR

Cycle = 28 days (no visit on Week 4)

	Pre-treatment	**Clinical Study Treatment**							**Post-treatment**	
	Screening Within 28 days (prior to Cycle 1)	**Cycle 1** (+/- 3 days)			**Cycle 2** (+/- 3 days)			**Remaining Cycles** (+/- 3 days)	**End of Treatment**	**Follow-up**
Week		**W1**	**W2**	**W3**	**W1**	**W2**	**W3**	**W1**	**Within 30 days of last drug dose**	**Every 6 months until death , LTF, or completion of long-term follow-up**
Informed consent and HIPAA waiver	X									
Demographics	X									
Medical history	X									
Urine or serum pregnancy test[a]	X									
Concurrent medications[m]	X	X			X			X	X	
Physical exam[g,m]	X	X[e]			X			X	X	
Vitals[h,m]	X	X	X[n]	X[n]	X	X[n]	X[n]	X	X	
ECOG performance status[m]	X	X[e]			X			X	X	
Adverse event evaluation[o]	X	Ongoing							X	
CBC w/differential[m]	X	X[e]			X			X	X	
CMP[j,m]	X	X[e]			X			X	X	
PTT	X									
PT/INR	X	X[e]								
Urinalysis	X									

Serum for correlative studies[b,m]		X			X			X	X	
Ascites for correlative studies[k]		X	X	X	X	X	X	X	X	
Radiologic evaluation by CT and tumor measurements by RECIST 1.1	X						X[c]	X[d]	X	X[f]
Survival status										X[l]
Nintedanib dispensing[i]		X			X			X		
Nintedanib compliance assessment					X			X	X	

a: In women of child-bearing potential; within 7 days of study drug administration and as clinically indicated throughout participation in the study

b: Serum sample will be collected and assayed for VEGF levels and stored for future study. At the C1D1 timepoint, collect serum after subject eligibility confirmation but prior to first nintedanib dose. At all time-points, serum should be collected prior to nintedanib dosing.

c: Within 7 days of anticipated completion of cycle 2

d: Within 7 days of anticipated completion of every two cycles) (e.g. cycles 4, 6, 8)

e: Not required if screening procedure done w/in 7 days of C1D1 per section 5.5

f: For subjects with disease control and who discontinue study therapy due to toxicity or reasons other than progressive disease, every effort will be made to obtain imaging studies and tumor assessments every 8 weeks (+/- 2 weeks) until documented progression or the start of new anti-cancer therapy

g: Physical exam: includes height (at screening only); Weight; body surface area (BSA).

h: Vitals: temperature; pulse rate; respiratory rate; blood pressure, oxygen saturation

i: Nintedanib capsules should be swallowed whole (unopened, uncrushed) with a glass of approximately. 8 oz. /240 mL of water. Since subjects will be taking oral nintedanib twice daily, the dose interval should be every 12 hours at the same time every day, usually in the morning and the evening after food intake.

j: Direct bilirubin required if total bilirubin above normal

k: Ascites fluid to be collected and assayed for VEGF levels and stored for future study. The decision to remove ascites fluid by paracentesis is determined **as clinically indicated by the investigator** based on subject symptoms. If paracentesis is done as part of standard of care, then every attempt will be made to collect a portion of ascites fluid and store for possible future study

l: Subject's initial anti-cancer therapy following discontinuation of nintedanib treatment and survival status will be documented.

m. May be performed within 72 hours of Day 1 of each cycle unless otherwise noted

n Blood pressure (only) will be assessed on Day 8 and Day 15 (+/- 2 days) during the first 2 cycles of study treatment. Blood pressure assessment may be done at home by the subject or at another clinic (i.e. local pharmacy), and the research staff will be responsible for obtaining these results from the subject. Phone contact is acceptable.

o. AE evaluation should be performed on Day 8 and Day 15 (+/- 2 days) of Cycles 1 and 2 when the research staff is contacting the subject for BP results.

7. TREATMENT PLAN

7.1. Nintedanib Dosage and Administration

Research participants for this study will initiate treatment with 200mg of oral nintedanib twice per day. The capsules should be swallowed whole (unopened, uncrushed) with a glass of approximately 8 oz. /240 mL of water. Since subjects will be taking oral nintedanib twice daily, the dose interval should be every 12 hours at the same time every day, usually in the morning and the evening after food intake.

In case of a missed dose the subjects should not replace that dose, but proceed to the next scheduled dose when it is due. Each study cycle length is 28 days.

In the event of a treatment delay at the scheduled Day 1 of a cycle, Day 1 of that cycle will be delayed until study treatment is re-started. This may cause a cycle to extend to longer than 28 days. Day 1 will be defined as the day the treatment is re-started.

For dose selection and modifications, see Section 8.

7.1.1 **Nintedanib (BIBF 1120) Drug Supply**

Nintedanib capsules for oral administration are formulated as soft gelatin capsules in two dose strengths (100 mg or 150 mg) and is provided in 30 count bottle. 100 mg capsules are peach, opaque, oblong, soft capsules imprinted in black with the BI company symbol and "100".150 mg capsules are brown, opaque, oblong, soft capsules imprinted in black with the BI company symbol “150”. Nintedanib will be supplied by BI. To request nintedanib from Boehringer Ingelheim, IDS Pharmacy will complete the BI-provided Drug Supply Request Form. Drug inventory levels should be able to provide subjects with nintedanib for up to 4-8 weeks while waiting for additional ordered supplies. The LCI Investigational Drug Services Pharmacy will receive nintedanib capsules of 100mg; 150 mg dosage in study drug bottles containing 30 capsules each. The study drug bottles will have a label affixed containing study identification, product identification and quantity of capsules. Once the drug has been received, it must be kept in a secure, dry location. Study drug must be stored in study drug bottle at room temperature 25°C (77°F). Temperature excursions between 15° to 30°C (59° to 86°F) is permitted.

7.2. Treatment Compliance

Nintedanib will be dispensed to subjects with instructions to return study drug pill bottles to research staff. Study drug bottles will be returned to the dispensing pharmacy. Capsules will be counted by pharmacy staff or delegate and reported to the

applicable research designee. The number of capsules taken by the subject per cycle will be determined by these capsule counts.

The subject will be considered to be compliant with treatment if ≥75% of doses were taken during any given cycle and overall, unless protocol treatment is withheld for toxicity.

Subject compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol. At the discretion of the Sponsor-Investigator, a subject may be discontinued from protocol for non-compliance with follow-up visits or study drug.

7.3. Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment will continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw study consent
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the Investigator.

Note: In the event the criteria for the final analysis are met, and there are subjects who have not yet been discontinued from study treatment, they will continue to receive therapy beyond the date the criteria for the study final analysis are met and until one of the above criteria applies.

7.4. Drug Accountability

All study drugs will be stored at the investigational site in accordance with product labeling, Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP) requirements and will be inaccessible to unauthorized personnel.

The study bottles will be returned to the pharmacy from which it was dispensed. Pharmacy or a designee will count the number of pills and communicate that to the applicable research designee.

An adequate record of receipt, distribution, and return or destruction of all study drugs must be kept in the form of a Drug Accountability Form. The Investigator, or

responsible party designated by the Investigator, will maintain a careful record of the inventory using the Drug Accountability Form.

7.5. Destruction

At the end of the study, unused and/or partially used supplies of nintendanib will be destroyed according to LCI IDS pharmacy policies.

8. NINTEDANIB INTERRUPTION

8.1. Criteria for Interruption of Treatment with Nintedanib

Treatment with nintedanib will be interrupted according to the criteria listed in Table 1.

In the event of a treatment delay at the time of Day 1 of a cycle, Day 1 of that cycle will be delayed until study treatment is re-started. This may cause a cycle to extend to longer than 28 days.

Table 1: Criteria for interrupting treatment with nintedanib due to an adverse event

If at least one criterion is met, nintedanib will be interrupted:
□ nausea of CTCAE grade ≥ 3 despite supportive care □ vomiting of CTCAE grade ≥ 2 despite supportive care □ diarrhea of CTCAE grade ≥ 2 for more than 3 consecutive days despite supportive care □ AST and/or ALT elevations of > 2.5 x ULN in conjunction with bilirubin of > 1.5 x ULN □ AST and/or ALT elevations of > 5x ULN □ other non-hematological adverse event of CTCAE grade ≥ 3 considered drug-related □ Neutropenia grade 3 or 4 and fever > 38.5°C □ Neutropenia CTCAE grade 4 for more than 7 days without fever □ Platelets <50,000mm³ with bleeding □ High blood pressure; SBP >170 mm Hg, or DBP >100 mm Hg □ Clinically significant bleeding, CTCAE grade 3 or 4, or grade 2 for 3 or more days

8.2. Criteria to Restart Treatment with Nintedanib

A research participant is eligible to restart nintedanib if all criteria listed in Table 2 are met.

If a subject must interrupt intake of nintedanib due to an adverse event for more than 14 days, the decision to restart treatment with nintedanib needs to be discussed and agreed upon between the sponsor-investigator and the treating physician.

Table 2: Criteria to assess eligibility to restart nintedanib treatment

All criteria must be met in order to restart nintedanib, meaning AEs have to return to Grade 1 or baseline (exception is nausea- see below).
□ nausea CTCAE grade ≤ 2 □ vomiting CTCAE grade ≤ 1 □ diarrhea CTCAE grade ≤ 1 □ AST and ALT < 2.5 x ULN; bilirubin < 1.5 x ULN □ no other non-hematological adverse event grade CTCAE ≥ 3 which is considered drug-related □ *Neutropenia CTCAE grade ≤ 1, without fever or equal to the subject's pre-therapy value at study enrolment □ *Platelets CTCAE grade ≤ 1 or equal to the subject's pre-therapy value at study enrolment □ Blood pressure SBP<150 mm Hg; DBP <90 mm Hg □ Bleeding CTCAE grade 1 or less

8.3. Dose Adjustments of Nintedanib

As initial measure for the management of side effects (see section 9), treatment with nintedanib should be temporarily interrupted until the specific adverse reaction has resolved to levels that allow continuation of therapy. Nintedanib treatment will be resumed at a reduced dose. Dose adjustments in 100 mg increments per day (i.e. a 50mg reduction per dosing) based on individual safety and tolerability are recommended as described in Table 1. In case of further persistence of the adverse reaction(s), i.e. if a subject does not tolerate 100 mg twice daily, treatment with nintedanib should be discontinued.

The following dose levels will be used in case dose adjustments are required for management of toxicity (see Table 3).

Table 3: Nintedanib dose levels – example for starting dose of 200mg twice daily

Dose-level:	0	-1	-2	-3
Dose:	2 x 200 mg/day	2 x 150 mg/day	2 x 100 mg/day	discontinue treatment

Of note:
If the dose of nintedanib had to be reduced due to toxicity, the subject will stay on the lower dose level for the entire time of administration.

9. TREATMENT-RELATED ADVERSE EVENTS

9.1. Management of Adverse Events

Based on prior clinical studies with nintedanib, the sponsor investigator should anticipate that any or all of the following AEs could occur. The occurrence of AEs and SAEs should prompt immediate notification to appropriate agencies as outlined in Section 11.6-11.8.

As an initial measure for the management of side effects, treatment with nintedanib should be temporarily interrupted as outlined in Table 1 until the specific adverse reaction has resolved to levels that allow restarting of therapy. Nintedanib treatment may be resumed at a reduced dose as outlined in table 4. Dose adjustments in 100 mg steps per day (i.e. a 50 mg reduction per dosing) based on individual safety and tolerability are recommended as described in Table 4. In case of further persistence of the adverse reaction(s), i.e. if a subject does not tolerate 100 mg twice daily, treatment with nintedanib should be discontinued.

Table 4: Dose adjustments for Nintedanib

CTCAE* Adverse reaction	Dose adjustment
Diarrhea ≥ grade 2 for more than 7 consecutive days despite anti- diarrheal treatment** ***OR*** diarrhea ≥ grade 3 despite anti- diarrheal treatment**	<u>1st episode</u> Reduce dose from 200 mg twice daily to 150 mg twice daily <u>2nd episode</u> Reduce dose from 150 mg twice daily to 100 mg twice daily <u>3rd episode</u> Stop treatment
Vomiting ** ≥ grade 2 ***AND/OR*** Nausea ≥ grade 3 despite anti-emetic treatment**	
AST and/or ALT elevations of > 2.5 x ULN in conjunction with bilirubin of > 1.5 x ULN ***OR*** AST and/or ALT elevations of > 5x ULN	
Other non-haematological or haematological adverse reaction of ≥ grade 3	
Elevation of AST and/or ALT values to > 3 x ULN in conjunction with an increase of total bilirubin to ≥ 2 x ULN and ALKP < 2 x ULN	Unless there is an alternative cause established, nintedanib should be permanently discontinued

*CTCAE- v4.03: Common Terminology Criteria for Adverse Events
** see also section 9.2.

9.2. Additional Precautions for Nintedanib

- *Diarrhea*
  Diarrhea was the most frequently reported gastro-intestinal event and appeared in close temporal relationship with the administration of docetaxel in

the clinical trial LUME-Lung 1[10]. The majority of subjects had mild to moderate diarrhea. 6.3 % had diarrhea of grade ≥3 in combination treatment compared to 3.6 % treated with docetaxel alone. Diarrhea should be treated at first signs with adequate hydration and anti-diarrheal medicinal products, e.g. loperamide, and may require interruption, dose reduction or discontinuation of therapy with nintedanib.

- *Nausea and vomiting*
  Nausea and vomiting, mostly of mild to moderate severity, were frequently reported gastrointestinal adverse events in the clinical trial LUME-Lung 1 [10]. Interruption, dose reduction or discontinuation of therapy with nintedanib may be required despite appropriate supportive care. Supportive care for nausea and vomiting may include medicinal products with anti-emetic properties, e.g. glucocorticoids, anti-histamines or 5-HT3 receptor antagonists and adequate hydration.

  In the event of dehydration, administration of electrolytes and fluids is required. Plasma levels of electrolytes should be monitored, if relevant gastrointestinal adverse events occur.

- *Neutropenia and Sepsis*
  A higher frequency of neutropenia of CTCAE grade ≥ 3 was observed in subjects treated with nintedanib in combination with docetaxel as compared to treatment with docetaxel alone in the clinical trial LUME-Lung 1[10]. Subsequent complications such as sepsis or febrile neutropenia have been observed.
  Blood counts should be monitored during therapy, if nintedanib (BIBF 1120) is combined with a myelosuppressive agent.

- *Hepatic Function*
  The safety and efficacy of nintedanib has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Therefore, treatment with nintedanib is not recommended in such patients.

  Administration of nintedanib was associated with an elevation of liver enzymes (ALT, AST, ALKP (alkaline phosphatase), and bilirubin), with a potentially higher risk for female patients.

  These increases were reversible in the majority of cases and not associated with clinically manifest liver disorders. Hepatic transaminases, ALKP and

bilirubin levels are recommended to be closely monitored after start of therapy with nintedanib.

If relevant liver enzyme elevations are measured, interruption, dose reduction or discontinuation of the therapy with nintedanib may be required (Refer to Table 4).

Alternative causes of the liver enzyme elevations should be investigated and respective action should be taken as necessary. In case of specific changes in liver values (AST/ALT > 3 x ULN; total bilirubin ≥ 2 x ULN and ALKP < 2 x ULN) treatment with nintedanib should be interrupted. Unless there is an alternative cause established, nintedanib should be permanently discontinued.

- *Special populations*
  Nintedanib exposure increased linearly with patient age, was inversely correlated to weight, and was generally higher in patients of Asian race. This may result in a higher risk of developing liver enzyme elevations. Close monitoring is recommended in patients with several of these risk factors.
  In study 1199.13 (LUME-Lung 1), there was a higher frequency of SAEs in patients treated with nintedanib plus docetaxel with a body weight of less than 50 kg compared to patients with a weight ≥ 50 kg; however, the number of patients with a body weight of less than 50 kg was small. Therefore, close monitoring is recommended in patients weighing < 50 kg.

9.3. Rescue Medications and Additional Treatments

Rescue medication to reverse the actions of nintedanib is not available. Potential side effects of nintedanib should be treated symptomatically.

9.4. Restrictions

The following are not permitted during study treatment:

- Other anti-neoplastic investigational treatment for appendiceal cancer .
- Systemic antitumor therapy, including cytotoxic therapy, signal transduction inhibitors, immunotherapy, radiotherapy and hormonal therapy .
- Bone marrow transplant or stem cell rescue.
- Therapeutic anticoagulation with drugs requiring INR monitoring (except low-dose heparin and/or heparin flush as needed for maintenance of an in-dwelling intravenous device) or anti-platelet therapy (except for low-dose therapy with acetylsalicylic acid ≤ 325mg per day).

The following are permitted during study treatment and will require additional/close monitoring:

- Strong P-gp inhibitors may increase exposure to nintedanib (e.g. ketoconazole or erythromycin). In such cases patients should be monitored closely for tolerability of nintedanib. Management of side effects may require interruption, dose reduction or discontinuation of therapy with nintedanib.
- Strong CYP3A4 and P-gp inducers, including but not limited to rifampicin, carbamazepine, phenytoin, and St. John's Wort (please see Appendix B), may decrease exposure to nintedanib. Co-administration with nintedanib should be carefully considered and closely monitored. Use of herbal remedies is discouraged, and is permitted only with the specific assent of the Investigator. All herbal and vitamin supplement use must be carefully documented.
- Subjects taking narrow therapeutic index medications should be monitored proactively (e.g. phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporine, and digoxin).

10. DATA AND SAFETY MONITORING PLAN

10.1. Safety Monitoring

This protocol will be monitored according to the processes in effect for all Levine Cancer Institute investigator- initiated studies and the protocol-specific monitoring plan, and will abide by standard operating procedures set forth by both the Carolinas HealthCare System Office of Clinical and Translational Research and the Levine Cancer Institute Clinical Trials Office. It is the responsibility of the Sponsor-Investigator to monitor the safety data for this study. The Sponsor-Investigator, Statistician, and other team members as needed will meet regularly to monitor subject consents, enrollment and retention, safety data for all subjects [including adverse events (AE's) for all grades and attributions, serious adverse events (SAE's)], study drug administration, and validity/integrity of the data. Documentation of these meetings will be kept with study records. SAEs will be reported to the IRB per their requirements. Major protocol deviations that in the Investigator's judgment potentially caused harm to participants or others or indicate that the participants or others are at an increased risk of harm, or has adversely impacted data integrity will be reported to the IRB per their requirements. The Sponsor-Investigator will submit data to the LCI Data and Safety Monitoring Committee according to the overarching LCI Data and Safety Monitoring Plan.

10.2. Data Quality Assurance

This study will be organized, performed, and reported in compliance with the study protocol, standard operating procedures (SOPs) of the Levine Cancer Institute and Carolinas HealthCare System Office of Clinical and Translational Research, and other applicable regulations and guidelines (e.g. GCP).

Data will be collected on electronic Case Report Forms (eCRFs).

Subjects will be monitored by Levine Cancer Institute Research Monitors routinely for data quality. This monitoring will be done by comparing source documentation to the eCRFs. The study database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by the appropriate research personnel. Only authorized personnel will make corrections to the study database and all corrections will be documented in an electronic audit trail.

10.3. Communication Between Investigational Sites

Investigational sites will be required to report problems with study drug administration or any other problem that could affect the validity/integrity of the study data to the Sponsor-Investigator by email as soon as possible but within 2 business days of the Investigator learning of the event. All investigational sites will record AEs using the eCRFs and SAEs using the SAE reporting function in the CTMS to the Sponsor. SAEs will be reported to the Sponsor-Investigator within 24 hours of the Investigator learning of the event.

10.4. Clinical Trial Registration

This study will be registered on the National Library of Medicine/National Institutes of Health ClinicalTrials.gov website. This trial will be initially registered prior to enrollment of the first subject. Trial's progress and results will be updated as necessary, but at least once every 6 months. Summary results of the trial will be submitted to the ClinicalTrials.gov website within 12 months of final data collected of the primary endpoint.

11. SAFETY DATA COLLECTION, RECORDING AND REPORTING

11.1. Unanticipated Problem (UAP) Definition

An unanticipated problem (UAP) is any incidence, experience or outcome that is unexpected, given the information provided in research-related documentation (e.g Investigator's brochure, informed consent) and the study population characteristics

that is related or possibly related to participation in the research study and places the participant at an increased risk.

11.2. Adverse Event (AE) Definition

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a subject in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study drug. Pre-existing conditions that increase in frequency or severity or change in nature during or as a consequence of use of a drug in human clinical trials are also considered adverse events. Adverse events may also include pre- or post-treatment complications that occur as a result of protocol mandated procedures.

Any continuing medical condition or clinically significant laboratory abnormality with an onset date before the date of informed consent should be documented in the subject's medical records and/or research chart.

Examples of events not meeting the definition of an adverse event include:

- medical or surgical procedures
- pregnancy (unless this is associated with an SAE)
- relapse or progression of the underlying malignant disease

The relationship to study drug should be assessed using the following definitions:

Not Related: Evidence exists that the AE has an etiology other than the study drug (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication). This includes events that are considered remotely or unlikely related to study drug.

Related: A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies. In the case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective study drug treatment should not be considered as causally related in the context of AE reporting. This includes events that are considered possibly, probably, or definitely related to study drug.

All adverse events (including event name, grade, start/stop date and attribution) will be documented in the medical record and/or research chart and on the case report form for this protocol.

Adverse Events of Special Interest (AESI) Definition
The following will be considered an AESI:

- an elevation of ALT and / or AST > 5x ULN without bilirubin elevation measured in the same blood draw sample.
- an elevation of AST and/or ALT >2.5x ULN combined with an elevation of bilirubin to >1.5x ULN measured in the same blood draw sample.
- any gastrointestinal- and non-gastrointestinal perforation, leakage, fistula formation, abscess.

In such case the following additional information is recommended to be collected, documented in the respective comment field and narratives of the BI SAE Report Form, and forwarded to BI:

- location of perforation, leakage, fistula, abscess
- location/extent of abdominal tumour manifestations,
- imaging & reports (CT, ultrasound, endoscopy, pathology, etc)
- prior surgery (location, wound healing complications)
- concomitant diseases with GI involvement (eg, M Crohn, vasculitis, tuberculosis,
- diverticulitis)
- thromboembolic events (or predisposition)

Please refer to Appendix A for recommended procedures for drug induced liver injury.

11.3. AESIs are to be reported in an expedited manner similar as Serious Adverse Events, even if they do not meet any of the seriousness criteria and documented in the eCRF. Serious Adverse Event (SAE) Definition

An AE is to be considered serious if the Investigator (in consultation with the Sponsor-Investigator if needed) deems it as such and the event results in any of the following outcomes:

- Death (fatal);
- Life-threatening situation (subject is at immediate risk of death);
- Persistent or significant disability/incapacity;
- Requires or prolongs inpatient hospitalization (excluding those for study drug administration, protocol-related procedures, palliative or hospice care, or placement of an indwelling catheter, unless associated with other serious events;

- A congenital anomaly/birth defect in the offspring of a subject who received study drug;
- Or based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the afore listed outcomes from occurring (e.g. intensive treatment in an emergency room without hospitalization, blood dyscrasias or convulsions that do not result in hospitalization, development of drug dependency or drug abuse).

The following events do not meet the criteria for seriousness per ICH definition, but must be reported in the same manner as SAEs. Therefore, these events are considered serious for collection purposes:

- Drug exposure during pregnancy

Subjects may be hospitalized for administrative or social reasons during the trial. These and other hospitalizations planned at the beginning of the trial do not need to be reported as an SAE.

The severity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 in the eCRF.

An increase in grade to a pre-existing CTC toxicity after study treatment initiation will be recorded as an AE.

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an AE if they are judged clinically significant by the investigator.

11.4. Adverse Event and Deviation Reporting

11.4.1. Reporting to the Sponsor (LCI)

All adverse events from the time of study treatment initiation until 30 days after last dose of study drug (including event name, grade, start/stop date and attribution) will be documented in the medical record and/or research chart and recorded on the case report form for this protocol.

The investigator is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

Protocol-specified AESI are to be reported in an expedited manner similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria.

SAEs and AESIs must be reported to the Sponsor-Investigator within 24 hours of awareness via the CTMS.

Information not available at the time of the initial report which is received after the initial report must be documented on a follow-up SAE utilizing the same process described above for reporting the initial SAE/AESI. For expedited reporting involving drug exposure during pregnancy, a follow-up report to describe the outcome of the pregnancy is required within 24 hours of investigator awareness.

SAEs will be captured from the time of signing of the informed consent through 30 days after the date of the last study drug administration. SAEs and AESIs will be followed until clinical recovery is complete, laboratory tests have returned to baseline, or until there has been acceptable resolution of the event. This may at times cause the follow-up period for SAEs and AESIs to be greater than 30 days. The above referenced 30-day time period applies even if the subject is taken off treatment and initiates subsequent anti-cancer treatment during this time period. Similarly, the treating investigator is responsible for following the subject during the required follow-up period even if the subject lives elsewhere or has been released from his or her care.

Deviations from the investigational plan must be reported to the sponsor via entry into the CTMS as soon as they occur, but within no more than 10 business days of becoming aware of the event (as soon as possible for deviations reportable to the IRB).

11.4.2. Safety Reporting to the IRB

All events occurring during the conduct of a protocol and meeting the definition of an UAP or related and unexpected SAE will be reported to the IRB per their reporting requirements.

Protocol deviations that are determined by the Investigator to potentially cause harm to participants or others or indicate that the participants or others are at an increased risk of harm, or have adversely impacted data integrity will be reported promptly to the IRB per their reporting requirements.

11.4.3. Safety Reporting to Funding Company (Boehringer Ingelheim Pharmaceuticals Inc.)

During the conduct of the study the Sponsor-Investigator shall report all

i. SAEs,
ii. AESIs independent of their seriousness,
iii. and non-serious AEs which are relevant to a reported SAE or AESI
iv. Pregnancies

by fax or other secure method using BI IIS SAE form providing as much detail as possible (pregnancies using Pregnancy Monitoring Form) to the BI Unique Entry Point in accordance with the timelines specified below as per the Pharmacovigilance agreement.

- within five (5) calendar days of the Sponsor-Investigator's knowledge of initial and follow-up SAEs containing at least one (1) fatal or immediately life-threatening event;
- within ten (10) calendar days of the Sponsor-Investigator's knowledge of any other initial and follow-up SAEs
- Pregnancy Monitoring Forms shall be forwarded within seven (7) days of Sponsor-Investigator awareness of the pregnancy

BI Unique Entry Point:

Boehringer Ingelheim Pharmaceuticals, Inc
900 Ridgebury Road
Ridgefield, CT 06877
Fax: 1-203-837-4329
E-mail: PV_global_casemanagement@boehringer-ingelheim.com.

With receipt of follow-up information, all remaining fields on the SAE form are to be completed or updated.

The investigator does not need to actively monitor the study subjects for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) or AESI(s) that occurred after the adverse event reporting period as defined in Section 11.4.1 (including any protocol specified follow-up period/Residual effect period), it should be reported to BI if the investigator considers it as relevant to the BI study drug.

11.4.4 Other Reporting

The IRB and Boehringer Ingelheim Pharmaceuticals (BI) will be notified in writing of other events according to the following schedule:

Table 5: Reporting to IRB and BI

Event	Agency	Timeframe for Reporting
Minor changes to the investigational plan	IRB	Within 90 days of SI becoming aware of change
	BI	Prior approval needed
[redacted]		
Major changes to the investigational plan (also known as amendments)	IRB	Prior approval needed
	BI	Prior approval needed
[redacted]		
Annual Report	IRB	Annually at time of IRB approval
	BI	Annual IRB approval letter to be provided to BI.
[redacted]		
Final Report	IRB	Part of study termination submission
	BI	Within 60 days after study completion

12. MEASUREMENT OF EFFECT

12.1. Anti-tumor Effect – Solid Tumor

Response and progression will be evaluated in this study using the revised response evaluation criteria in solid tumors (RECIST) guideline version 1.1[1].

12.1.1. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All screening evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at screening, during treatment and follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

12.1.2. Response Criteria

Response will be evaluated using RECIST 1.1 Criteria.

Complete Response:

- Target lesion: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Non-target lesion: Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Partial Response:

- Target lesion: At least a 30% decrease in the sum of diameters of target, taking as reference the baseline sum diameters.
- Non-target lesion: Not applicable

Stable Disease:

- Target lesion: Neither sufficient shrinkage to qualify for a partial response, nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.
- Non-target lesion: Not applicable.

Progressive Disease:

- Target lesion: At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).
- Non-target lesion: *Unequivocal progression* (as described in RECIST version 1.1) of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

Non-Complete Response / Non-Progressive Disease:

- Target lesion: Not applicable
- Non-target lesion: Persistence of one or more non-target lesion(s)

Table 6: Summary of RECIST

Target Lesions	Non-target Lesions	New Lesions	Overall Response	Best Response for this Category also requires
CR	CR	No	CR	Documented at least once ≥ 4 weeks from baseline
CR	Non-CR/Non-PD	No	PR	Documented at least once ≥ 4 weeks from baseline
CR	Not evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	
SD	Non-PD or not all evaluated	No	SD	Documented at least once ≥ 4 weeks from baseline
Not all evaluated	Non-PD	No	NE	N/A
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression
CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, and
NE = inevaluable

Table 7: Overall Response for Subjects with Non-measurable disease only

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/ Non-PD	No	Non-CR/ Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

13. STATISTICAL CONSIDERATION

13.1 Sample Size

This study is a Simon (minimax) two-stage design that will enroll up to a total of 39 subjects. The primary endpoint is overall disease control. In the first stage, a total of 28 subjects in the evaluable population will be enrolled. Of these, if at least 8 should

achieve disease control (Section 13.1.1) the study will continue on to the second stage. In the second stage, 11 participants in the evaluable population (total of 39) will be enrolled. If at least 16 of the 39 total subjects enrolled achieve disease control then we will be able to reject the null hypothesis. The sample size of evaluable population for both Stage 1 and Stage 2 include participants who begin nintedanib therapy.

Given the lack of information of clear benefit of any therapy in the second line setting of subjects with appendiceal carcinoma, a disease control rate of 30% would be considered an inferred clinical historical rate. Alternatively, a 50% disease control rate which, if achieved, would be worthy of further investigation. Assuming a one-sided alpha = 0.10 significance level, this design will provide at least 90% power to reject the null hypothesis, assuming the true disease control rate is 50%.

Endpoint Definitions

13.1.1. Disease Control

Disease control will be determined for each subject as a binary variable indicating whether or not subjects with measurable disease achieve a best overall response of CR, PR, or SD as determined by RECIST 1.1 and subjects with non-measurable disease have at least one evaluable disease assessment indicating non-progressive disease.

13.1.2. Objective Response

Objective response will be determined for each subject as a binary variable indicating whether or not the subject achieved a best overall response of CR or PR as determined by RECIST 1.1.

13.1.3. Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from the start of nintedanib treatment to first occurrence of either progressive disease or death. Disease progression can be objectively determined as per Section 12 (RECIST 1.1) or progression can be subjective as determined by the investigator. Evidence for subjective progression must be documented in the medical records. For objective disease progression, the date of PD is the date of the radiologic assessment that identified RECIST-defined progressive disease. For subjective disease progression, the date of PD is the date that the clinician makes the determination of disease progression. If the subject died without documented disease progression, the date of progression will be the

date of death. For surviving subjects who do not have documented disease progression, PFS will be censored at the date of last radiologic assessment. For subjects who receive subsequent anti-cancer therapy prior to documented disease progression, PFS will be censored at the date of last radiologic assessment prior to the commencement of subsequent therapy. Subjects who have an initial PFS event immediately following 2 or more consecutive missed assessments will be censored at the date of the last assessment prior to those missed assessments. For subjects with only one missed assessment, the documented progressive disease status and assessment date will be used.

13.1.4. Six-Month Progression-Free Survival

Six-month progression-free survival will be determined for each subject as a binary variable indicating whether or not the subject is alive and progression free at 6 months. The criteria for a PFS event are defined in Section 13.1.3.

13.1.5. Overall Survival

Overall survival is defined as the duration from the start of nintedanib treatment to the date of death from any cause. Subjects who are alive or lost to follow-up at the time of the analysis will be censored at the last known date they were alive.

13.1.6. Safety Endpoints

Safety endpoints will include treatment administration, AEs, SAEs, deaths while on study therapy, and blood pressure. Treatment administration will be determined for each subject in terms of cumulative and average daily dose of nintedanib administration (adjusting for dose delays and reductions). Additionally, the relative dose intensity will be calculated for each subject in terms of the actual daily dose administered as a percent of the intended daily dose.

13.2. Analysis Populations

The response-evaluable population for the analysis of objective response will include enrolled subjects with measurable disease at baseline. The evaluable population for the analysis of disease control, all other secondary endpoints, and safety endpoints will include subjects who begin nintedanib treatment. The sample size requirements for

Stage 1 and 2 described above pertain to the evaluable population for the analysis of disease control.

13.3. Analysis Methods

13.3.1. Timing of Analysis

The Stage 1 analysis will be conducted after the best overall response for all Stage 1 evaluable subjects has been determined. The primary analysis of Stage 2 will be conducted after the best overall response of all evaluable subjects has been determined. An updated analysis will be conducted after all enrolled participants have been on study for at least one year. The final analysis will be conducted after the PFS censoring rate reduces to 20% or after all subjects have been on study for at least 3 years, whichever occurs first.

13.3.2. Subject Disposition

An accounting of all consenting subjects will be provided at the end of the study. This will include a breakdown of subjects who consented, were treated, discontinued treatment, died, and were lost to follow-up or withdrew consent.

13.3.3. Baseline Subject and Disease Characteristics

A summary of subject demographics and disease-related characteristics will be completed and assessed.

13.3.4. Efficacy Analyses

13.3.4.1. Primary Analysis

Disease control rate will be estimated with the corresponding 95% Clopper-Pearson confidence interval. Evaluation of the primary objective will be made based on the rejection regions described in Section 13.1.

13.3.4.2. Secondary Analyses

Objective response rate and 6-month PFS rate will be estimated with the corresponding 95% Clopper-Pearson confidence interval.

Progression-free survival and overall survival rates will be estimated using Kaplan-Meier techniques.

Multivariable regression models (logistic regression for binary variables and Cox proportional hazards models for time to event variables) will be used to evaluate the impact of correlative biomarkers, and baseline subject and disease characteristics on outcomes. Additionally, nintedanib exposure will be considered as a covariate.

13.3.5. Safety Analyses

Treatment administration will be summarized descriptively in terms of cumulative and average daily dose of nintedanib administration (adjusting for dose delays and reductions). Additionally, the relative dose intensity will be calculated in terms of the actual daily dose administered as a percent of the intended daily dose. Incident rates for treatment-emergent adverse events, SAEs, and deaths while on study therapy will be summarized.
Treatment-emergent adverse events are defined as follows:

- An adverse event that occurs after treatment start that was not present at the time of treatment start; or
- An adverse event that increases in severity after treatment start if the event was present at the time of treatment start

13.3.6. Exploratory Analyses

An evaluation of serum VEGF, ascites VEGF, hypertension and paracentesis frequency will be made. This will include summaries of expression levels, baseline prevalence, and correlations between these biomarkers and response to therapy. Additional exploratory analysis will be conducted as deemed necessary.

13.4. Interim Analyses

An analysis of disease control will be conducted after the best overall response of the first 28 evaluable participants has been determined.

14. STUDY COMPLETION

14.1. Completion

The study will be considered complete when one or more of the following conditions is met:

- All subjects have died and/or withdrawn from the study.
- All subjects have discontinued from the study.
- The IRB, LCI DSMC, or Sponsor-Investigator discontinues the study because of safety considerations.
- The Sponsor-Investigator defines an administrative or clinical cut-off date.

14.2. Termination

The study will be terminated when one or more of the following conditions occur:

If risk-benefit ratio becomes unacceptable owing to, for example,

- Safety findings from this study (e.g. SAEs)
- Results of any interim analysis
- Results of parallel clinical studies
- Results of parallel animal studies (e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The Sponsor-Investigator has the right to close the trial at any site and at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions must be informed as applicable according to local law.
- In case of a partial study closure, ongoing subjects, including those in follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 5.4.2.

15. RETENTION OF RECORDS

Essential documentation (e.g. adverse events, records of study drug receipt and dispensation), including all IRB correspondence, will be retained for at least 2 years after the investigation is completed. Documentation will be readily available upon request.

16. ETHICAL AND LEGAL ISSUES

16.1. Ethical and Legal Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate agencies (e.g. IRB) will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations. Any extension or review of any amendment of protocol and annual renewal of IRB approval must be obtained and forwarded to Boehringer Ingelheim.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the Investigators may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by the Sponsor-Investigator without discussion and agreement by Boehringer Ingelheim. However, the Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior approval from applicable agencies. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the appropriate agencies. Any deviations from the protocol must be explained and documented by the Investigator.

The Sponsor-Investigator is responsible for the conduct of the clinical trial at the sites in accordance with Good Clinical Practice and the Declaration of Helsinki. The Sponsor-Investigator is responsible for overseeing the treatment of all study subjects.

The Sponsor-Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all applicable regulations and guidelines regarding clinical trials both during and after study completion.

The Sponsor-Investigator will be responsible for assuring that all the required data will be collected and properly documented.

16.2. Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.
2. Cortina R, McCormick J, Kolm P, Perry RR. Management and prognosis of adenocarcinoma of the appendix. *Diseases of the colon and rectum.* 1995;38(8):848-852.
3. Tejani MA, ter Veer A, Milne D, et al. Systemic therapy for advanced appendiceal adenocarcinoma: an analysis from the NCCN Oncology Outcomes Database for colorectal cancer. *J Natl Compr Canc Netw.* 2014;12(8):1123-1130.
4. Borazanci E, Millis SZ, Feldman RA, Ghazalpour A, Ramanathan RK, Von Hoff DD. Potential actionable targets in appendiceal cancer detected by immunohistochemistry (IHC), fluorescent in situ hybridization (FISH), and mutational analysis. *ASCO Meeting Abstracts.* 2014;32(15_suppl):4143.
5. Jimenez WA, Sardi A, Ledakis P, Nieroda C, Sittig M, Gushchin V. The role of VEGFR-2 expression in outcomes and survival of patients with peritoneal carcinomatosis from appendiceal cancer. *European Journal of Surgical Oncology (EJSO).* 2013;39(12):1415-1422.
6. Chang MS, Byeon SJ, Yoon SO, et al. Leptin, MUC2 and mTOR in appendiceal mucinous neoplasms. *Pathobiology.* 2012;79(1):45-53.
7. Nascimento I, Schaer R, Lemaire D, et al. Vascular endothelial growth factor (VEGF) levels as a tool to discriminate between malignant and nonmalignant ascites. *APMIS.* 2004;112(9):585-587.
8. Gotlieb WH, Amant F, Advani S, et al. Intravenous aflibercept for treatment of recurrent symptomatic malignant ascites in patients with advanced ovarian cancer: a phase 2, randomised, double-blind, placebo-controlled study. *Lancet Oncol.* 2012;13(2):154-162.
9. Hilberg F, Roth GJ, Krssak M, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. *Cancer research.* 2008;68(12):4774-4782.
10. Reck M, Kaiser R, Mellemgaard A, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. *Lancet Oncol.* 2014;15(2):143-155.
11. Stopfer P, Rathgen K, Bischoff D, et al. Pharmacokinetics and metabolism of BIBF 1120 after oral dosing to healthy male volunteers. *Xenobiotica.* 2011;41(4):297-311.
12. Mross K, Stefanic M, Gmehling D, et al. Phase I Study of the Angiogenesis Inhibitor BIBF 1120 in Patients with Advanced Solid Tumors. *Clinical Cancer Research.* 2010;16(1):311-319.
13. Reck M, Kaiser R, Eschbach C, et al. A phase II double-blind study to investigate efficacy and safety of two doses of the triple angiokinase inhibitor BIBF 1120 in patients with relapsed advanced non-small-cell lung cancer. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.* 2011;22(6):1374-1381.
14. Hanna NH, Kaiser R, Sullivan RN, et al. Lume-lung 2: A multicenter, randomized, double-blind, phase III study of nintedanib plus pemetrexed versus placebo plus pemetrexed in patients with advanced nonsquamous non-small cell lung cancer (NSCLC) after failure of first-line chemotherapy. *ASCO Meeting Abstracts.* 2013;31(15_suppl):8034.
15. Ledermann JA, Hackshaw A, Kaye S, et al. Randomized Phase II Placebo-Controlled Trial of Maintenance Therapy Using the Oral Triple Angiokinase Inhibitor BIBF 1120

After Chemotherapy for Relapsed Ovarian Cancer. *Journal of Clinical Oncology.* 2011;29(28):3798-3804.

16. du Bois A, Kristensen G, Ray-Coquard I, et al. AGO-OVAR 12: a randomized placebo-controlled GCIG/ENGOT-Intergroup phase III trial of standard frontline chemotherapy +/− nintedanib for advanced ovarian cancer. Abstracts from the 18th International Meeting of the European Society of Gynaecological Oncology (ESGO), 19–22 October 2013, Liverpool, UK. Int J Gynecol Cancer. 2013;23(8 Suppl 1).
17. Van Cutsem E, Prenen H, Guillen-Ponce C, Bennouna J, Di Benedetto M, Bouche O, et al. A Phase I/II Open-label, Randomised Study of BIBF 1120 Plus mFOLFOX6 Compared to Bevacizumab Plus mFOLFOX6 in Patients with Metastatic Colorectal Cancer. Eur J Cancer 2011; 47 (suppl2): 8, LBA14.
18. Cheng A-L, Yen C-J, Kim T-Y, Feng Y-H, Chao Y, Lin D-Y et al. Efficacy and safety of nintedanib versus sorafenib in Asian patients with advanced hepatocellular carcinoma (HCC): A randomized phase II trial. J Clin Oncol 2015; 33 (suppl 3, abstr 339).
19. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med.* 2014;370(22):2071-2082.

APPENDICES

APPENDIX A

Recommended Procedures for the follow-up of a potential DILI case (Hy's Law case) in IIS with nintedanib

Introduction

Drug-induced liver injury

Drug-induced liver injury (DILI) has been the most frequent single cause of safety-related drug marketing withdrawals for the past 50 years (e.g., iproniazid), continuing to the present (e.g., ticrynafen, benoxaprofen, bromfenac, troglitazone, nefazodone). Accordingly, detection of drug-induced liver injury of an investigational compound has become an important aspect of patient´s safety guarding in drug development.

The US-FDA has published a Guidance for Industry entitled, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" which outlines the detection, evaluation, follow-up and reporting of drug-induced liver injury in clinical trials. Drugs that have the potential for inducing severe liver injury may be identified by marked peak aminotransferase elevations (10x-, 15xULN), or the combination of hepatocellular injury (aminotransferase elevation ≥3xULN) and altered liver function (hyperbilirubinemia ≥2xULN) which is defined as potential "Hy´s law case" if not explained by other causes including evidence of biliary obstruction (i.e., significant elevation of alkaline phosphatase, ALP, >2X ULN) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis, concomitant use of other known hepatotoxic drugs). This constellation predicts a poor outcome and although very rare, these potential cases have to be well characterized as soon as being identified as other confounding conditions may be the cause.

In further consideration of this FDA Guidance, any potential "Hy's Law case" has to be reported in an expedited manner to the FDA (i.e., even before all other possible causes of liver injury have been excluded) and be followed-up appropriately. The follow-up includes a detailed clinical evaluation and identification of possible alternative etiologies for the "Hy´s Law case" constellation such as concomitant diseases (e.g. Hepatitis B) and/or other concomitant therapies that might potentially be hepatotoxic.

Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety.

The concept below has been worked out by Boehringer Ingelheim (BI) in order to guard patient´s safety and to respond to regulatory requirements. It is the basis for all clinical studies and should be applied as appropriate.

Definition

The following changes in the laboratory values are considered to be a protocol-specific significant adverse event for all subjects:

- an elevation of ALT and / or AST > 5x ULN without bilirubin elevation measured in the same blood draw sample
- an elevation of AST and/or ALT >2.5 fold ULN combined with an elevation of bilirubin to >1.5 fold ULN measured in the same blood draw sample.

These definitions are in line with the current dose reduction recommendations as outlined in all study protocols for BIBF 1120.

Subjects showing these laboratory abnormalities need to be followed up until the protocol specific retreatment criteria have been met.

Procedures

1. Protocol-specified significant events are to be reported in an expedited manner similar as Serious Adverse Events, even if they do not meet any of the seriousness criteria and documented in the eCRF

2. Replication of the following laboratory tests for confirmation within 48 hours:

    - AST, ALT,
    - bilirubin measurement (total and direct bilirubin)
    - Alkaline Phosphatase
    - Haptoglobin
    - Complete blood count and cell morphology
    - Reticulocyte count
    - CK
    - LDH

    The results of these repeated laboratory tests must be reported immediately via the SAE form to BI.

3. An evaluation of the subject within 48 hours with respect to but not limited to:

    - Abdominal ultrasound or clinically appropriate other imaging and investigations adequate to rule out biliary tract, pancreatic, intra- or extrahepatic pathology, e.g. bile duct stones, neoplasm, hepatic tumour involvement, biliary tract, pancreatic or intrahepatic pathology, vascular

hepatic conditions such as portal vein thrombosis or right heart failure. These data need to be collected, documented in the respective SAE form, updated and forwarded to BI

- detailed history of current symptoms and concurrent diagnoses and medical history

- detailed history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations and eg steroids as concomittant suppportive treatment), alcohol use, recreational drug use, and special diets detailed history of exposure to environmental chemical agents

4. In case that both imaging and laboratory value did not unequivocally confirm cholestasis as the reason of ALT / AST increase, in particular if Alkaline Phosphatase < 2x ULN, then please complete the following laboratory tests:

   - Clinical chemistry
     alkaline phosphatase, cholinesterase (either plasma or red blood cell), albumin, PT or INR, CK, CK-MB, coeruloplasmin*, α-1 antitrypsin*, transferrin, ferritin, amylase*, lipase*, fasting glucose*, cholesterol, triglycerides
   - Serology
     Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG)*, Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive)*, Anti-Smooth Muscle antibody (titer)*, Anti-nuclear antibody (titer)*, Anti-LKM (liver-kidney microsomes) antibody*, Anti-mitochondrial antibody*, Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM)
   - Hormones, tumormarker
     TSH*
   - Haematology
     Thrombocytes*, eosinophils*

     *If clinically indicated and in case that additional investigations are needed (e.g immunocompromised patients.)

5. Initiate close observation of all subjects with elevated liver enzyme and bilirubin elevations by repeat testing of ALT, AST, bilirubin (with fractionation into total and

direct) and AP at least weekly until the laboratory values return to normal or to the values as defined in the protocol.

6. In case that transaminases and/or bilirubin increase despite cessation of the experimental therapy, more frequent intervals will be warranted.

   Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices.

APPENDIX B: STRONG PGP INHIBITORS

abiraterone	Lopinavir and lopinavir-ritonavir
Amiodarone	Mefloquine
Atorvastatin	Mirabegron
Azithromycin (systemic)	Nicardipine
Carvedilol	Nilotinib
Clarithromycin	Ombitasvir
Cobicistat and cobicistat containing coformulations	Paritaprevir-ritonavir
Crizotinib	Progesterone
Cyclosporine (systemic)	Propranolol
Daclatasvir	Quinidine
Darunavir	Quinine
Dipyridamole	Ranolazine
Dronedarone	Reserpine
Eliglustat	Ritonavir and ritonavir containing coformulations
Erythromycin (systemic)	Saquinavir
Flibanserin	Simeprevir
Grapefruit juice and grapefruit	Sunitinib
Ibrutinib	Tacrolimus (systemic)
Itraconazole	Tamoxifen
Ivacaftor	Telaprevir
Ketoconazole (systemic)	Vandetanib
Lapatinib	Vemurafenib
Ledipasvir	Verapamil
Lomitapide	

STRONG PGP INDUCERS

Amprenavir
Carbamazepine
Clotrimazole
Dexamethasone
Fosamprenavir
Indinavir
Morphine
Nelfinavir
Phenobarbital
Phenothiazine
Phenytoin
Prazosin
Retinoic acid
Rifampin
Ritonavir
Saquinavir
St John's wort
Tipranavir