德琪医药科技
ANTENGENE CORPORATION

Clinical Trial Protocol

Name of Product:	**ATG-008**
Protocol Number:	**ATG-008-HCC-001**
Protocol Title:	**An Open-label Phase 2 Trial of Dual TORC1/TORC2 Inhibitor ATG-008 in HBV+ Advanced Hepatocellular Carcinoma (HCC) Subjects Who Have Received at Least One Prior Line of Systemic Therapy (TORCH)**
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English Translated Version

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PROTOCOL SYNOPSIS

Study Title

An Open-label Phase 2 Trial of Dual TORC1/TORC2 Inhibitor ATG-008 in HBV+ Advanced Hepatocellular Carcinoma (HCC) Subjects Who Have Received at Least One Prior Line of Systemic Therapy (TORCH)

Indication

Hepatitis B virus (HBV) positive, unresectable HCC subjects who have received at least one prior line of systemic therapy.

Objectives

The primary objectives of the trial are:

- To evaluate pharmacokinetics (PK), safety, tolerability and overall response rate (ORR) of ATG-008 in HBV+ HCC subjects who have received at least one prior line of systemic therapy.

The secondary objectives of the trial are:

- To evaluate overall survival (OS)
- To evaluate time to progression (TTP)
- To evaluate progression-free survival (PFS)
- To evaluate disease control rate (DCR)
- To evaluate duration of response (DOR)
- To evaluate time to response (TTR)
- To evaluate survival rate

Trial Design

ATG-008-HCC-001 is an Asian multi-regional clinical trial (MRCT) in which ATG-008 will be administered orally to hepatitis B positive (HBV+) HCC subjects who have received at least one prior line of systemic therapy. It is designed as an open-label phase 2 trial evaluating the pharmacokinetics (PK), safety, tolerability and efficacy of oral ATG-008 administered daily until the radiologic disease progression (according to RECIST 1.1) or intolerable toxicity.

Study Population

Number and Population of Subjects:

Approximately 30 HBV+, unresectable HCC subjects who have received at least one prior line of systemic therapy will be enrolled in this trial, including 6 at the dose of 15mg and 24 at the dose of 30mg.

According to the previous study results, the sponsor plans to continue to enroll approximately 40 hepatitis B virus (HBV) positive, unresectable HCC subjects who have previously received at least one prior line of systemic therapy. Among which, approximately 20 subjects will receive oral ATG-008 at an initial dose of 45 mg, once daily (QD) and another approximately 20 subjects will receive oral ATG-008 at an initial dose of 20 mg, twice daily (BID). The pharmacokinetic (PK) samples will be collected from 10 subjects each in the two dose groups.

If the overall response rate (ORR) of tumor is greater than 15% in the study dose group (45 mg/QD or 20 mg/BID), then this study will be expanded to enroll additional approximately 110 subjects using ORR as the primary study endpoint, to further evaluate the efficacy and safety of ATG-008.

Inclusion Criteria:

1. Male or female aged from 18 to 70 years (inclusive) at the time when the ICF is signed.
2. Confirmed pathologic or radiologic diagnosis of HCC according to the American Association for the Study of Liver Disease (AASLD) guidelines.
3. Unresectable stage B (intermediate) or C (advanced) HCC according to the Barcelona Clinic Liver Cancer (BCLC) staging. If stage B, the subject must have progressed after, or not be eligible for, surgical or locoregional therapy.
4. There is at least one measurable lesion according to RECIST 1.1 criteria.
5. HBV+ is defined as chronic HBV infection or a history of HBV infection, based on any of the following serologic results: HBcAb+, HBsAg+, HBV-DNA+.
6. Received at least one prior line of systemic therapy (with radiologic disease progression during or following sorafenib and/or chemotherapy). Subjects with alternative treatments such as regorafenib and/or anti PD-1 antibodies etc. approved by local health authorities are allowed to enter study if they meet all other inclusion/exclusion criteria.
    a. Chemotherapy includes FOLFOX (fluorouracil, leucovorin and oxaliplatin) or any other platinum-containing regimen.
    b. Chemotherapy ≥ two cycles.
7. ECOG performance status score of 0 or 1.
8. Satisfactory serum chemistry results, evidenced by the following:
    a. AST (SGOT) and ALT (SGPT) ≤ 5x upper limit of normal (ULN).
    b. Total bilirubin ≤ 2 × ULN.
    c. Creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 50 mL/min.
    d. Lipase and amylase ≤2 x ULN;
9. Adequate bone marrow function, evidenced by the following:
    a. Absolute neutrophil count (ANC) ≥ 1.5×10^9 cells/L.
    b. Platelets ≥ 75×10^9 cells/L.
    c. Hemoglobin ≥ 9 g/dL.
10. Coagulation function: international normalized ratio (INR) ≤2.0, prothrombin time (PT) ≤1.5 x ULN;
11. Child-Pugh A and B7 and hepatic encephalopathy scored as 1 point;
12. Except hearing loss and alopecia, all toxicities caused by previous anti-tumor therapies must recover to ≤ Grade 1 (based on NCI-CTCAE Version 4.03);
13. Male subjects (including those who have had a vasectomy) must agree to use a condom during sexual intercourse with females of child-bearing potential, and shall not conceive a child starting from the time of ICF signature, while on study medication, and for 3 months after the last dose of study drug.
14. Female subjects of child-bearing potential must have both of the following:
    a. Agree to the use of two study physician-approved contraceptive methods simultaneously, or practice complete abstinence starting at the time of ICF signature, while on study medication, and for 28 days following the last dose of study drug.
        i. True abstinence: When this is in line with the preferred and usual lifestyle of

the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

ii. Acceptable contraceptive methods include: Oral, injectable, or implantable hormonal contraceptive; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner, together with at least one barrier method.

b. Have negative serum pregnancy test result at screening, confirmed by negative urine pregnancy test within 72 hours prior to first dose of study drug (if serum test occurred > 72 hours from first dose); pregnancy test must have a sensitivity of at least 25 mIU/mL.

Exclusion Criteria:

The presence of any of the following will exclude a subject from enrollment:

1. Intolerant to sorafenib/regorafenib, e.g.:

   a. The drug is discontinued due to adverse events;

   b. The related adverse events of Grade ≥2 continued/relapsed after supportive treatment and/or dose reduction or dose interruption at least 7 days;

   c. The treatment course is less than 21 days within 28 days before discontinuation; the lowest daily dose of sorafenib is 400 mg/day.

2. Medical history of hepatic encephalopathy;
3. Central nervous system metastases;
4. Treatment with molecular targeted therapies such as sorafenib, regorafenib or lenvatinib within 4 weeks before screening;
5. Treatment with locoregional HCC therapy (including but not limited to TACE, RFA), systemic chemotherapy, hormonal therapy (e.g., tamoxifen), traditional Chinese medicine with anti-tumor effects, or clinical investigational drugs within 4 weeks prior to Screening;
6. Tested positive for both HBV and hepatitis C virus (HCV).
   a. HCV positive is defined as anti-HCV or HCV-RNA positive
7. Life expectancy of less than 3 months.
8. Prior therapy with mTOR (TORC1 and/or TORC2) inhibitors including sirolimus, temsirolimus, everolimus, and other investigational or approved mTOR/PI3K/AKT inhibitors.
9. Have received major surgery within 4 weeks before screening or plan to receive major surgery during study period;
10. Receiving active, ongoing treatment with systemic corticosteroids at a prednisone equivalent dose of ≥ 10 mg daily or other systemic immune system modulators. The exceptional cases of such criterion are listed as follows:

    a. Intranasal, inhaled and topical steroids or local steroid injection (e.g., intra-articular injection);

    b. Prednisone not more than 10 mg/day or its equivalent physiological dose of systemic corticosteroids;

    c. Steroids as the prophylatic medication of allergic reactions (pretreatment before CT

scan);

11. Imaging test results showing main portal venous tumor thrombus, inferior vena cava tumor thrombus, or heart involvement;
12. Uncontrolled diabetes, defined as HbA1c > 7%.
13. Prior organ transplant.
14. Uncontrolled pleural effusion or pericardial effusion (with clinical symptoms, fluctuation of effusion or requiring repeated drainage, oral diuretics etc.) at screening; Ascites at screening, which can be detected by physical examination, or clinical symptoms caused by ascites, or requiring special treatment such as repeated drainage, peritoneal drug perfusion etc. (subjects who only have a small amount of ascites which can be detected by imaging examination can be enrolled).
15. Persistent diarrhea or malabsorption ≥ National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03) grade 2, despite medical management, or any significant gastrointestinal disorder that could affect the absorption of study drug.
16. Medical history of active upper gastrointestinal hemorrhage, ulcer or esophageal varices associated with hemorrhage or such diseases within 6 months;
17. Subjects who have medical history of human immunodeficiency virus infection and/or acquired immunodeficiency syndrome;
18. Concurrent active second malignancy for which the subject is receiving therapy, excluding non-melanomatous skin cancer, non-progressive prostate cancer treated with hormonal therapy, or carcinoma in situ of the cervix. Any cancer curatively treated >5 years prior to entry is permitted.
19. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection (e.g., tuberculosis) requiring antibiotic, antifungal, or antiviral therapy (other than anti-HBV therapy), acute or chronic pancreatitis or psychiatric illness/social situations that would limit compliance with study requirements.
20. Subjects who have clinically significant cardiovascular diseases such as Grade Ⅱ and above cardiac dysfunction (New York Heart Association criteria), ischaemic heart diseases (e.g., myocardial infarction or unstable angina pectoris), clinically significant supraventricular or ventricular arrhythmia, uncontrolled hypertension (systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg), echocardiography showing ejection fraction <50%, QTc interval >450 ms (male), QTc interval >470 ms (female);
21. The subject's complications or other conditions may affect protocol compliance or make the subjects unsuitable to participate in this study at the discretion of the investigator.

Study Rationale

- **Clinical efficacy: compared to the study results of Celgene, the current preliminary clinical study data of this study showed that ATG-008 treatments with 15 mg and 30 mg were effective, but the expected tumor control rate had not been observed yet. It was preliminarily considered that the best dose range of ATG-008 might have not been achieved.**

According to the results of study CC-223-ST-001-B which has been completed by Celgene, the

ORR of solid tumor HCC cohort was 5.7% (3/53), among which, the best efficacy of 3 subjects (all had positive HBV) was PR and 2 of them were treated with 45 mg/QD ATG-008 (the maximum tolerated dose [MTD] of ATG-008 monotherapy was 45 mg/day, the intolerable dose was 60 mg/day).

As of 18 Jul 2019, the preliminary clinical study data showed that this study enrolled a total of 35 HCC subjects (all were Asian; among which, 15 subjects were from Chinese mainland, 13 from Korea and 7 from Taiwan. 7 subjects received oral ATG-008 at the initial daily dose of 15 mg and 28 subjects received 30 mg). Among 35 subjects, 1 subject achieved PR, 14 subjects achieved SD, 19 subjects achieved PD and 1 subject still received the first cycle of treatment and no efficacy evaluation has been performed yet. The survivors accounts for approximately 65.7% (23/35). The diameter of the targeted lesions of tumors decreased after treatment from baseline in 38.2% (13/34) subjects. Currently, subjects who received the longest treatment had completed 11 cycles of treatment.

- **Clinical safety: the safety profile currently observed in this study was similar to the results of foreign studies completed by Celgene and that of mTOR targeted drugs**

The most common related TEAEs in study CC-223-ST-001 completed by Celgene were decreased appetite (64.2%), diarrhea (60.4%), fatigue (60.4%), hyperglycemia (60.4%), nausea (50.9%), aspartate aminotransferase increased (43.4%), and pruritus (34%).

No suspected and unexpected serious adverse reactions (SUSAR) were reported in this study. One case of DLT was observed in 15 mg dose group and no DLT in 30 mg group. The most frequently reported study drug-related TEAEs were skin rash and hyperglycemia (45.7% each), decreased appetite and pruritus (31.4% each), diarrhea and stomatitis (28.6% each), weight loss (22.9%), fatigue and platelet count decreased (20.0% each), white blood cell count decreased, mouth ulceration and proteinuria (17.1% each), nausea, hepatic dysfunction and hand-foot syndrome (14.3% each), discomfort and AST elevated (11.4% each).
As ATG-008 is firstly and orally administered hepatitis B virus (HBV) positive, HCC Asian subjects who have previously received at least one prior line of systemic therapy in this study, the overall safety profile of ATG-008 is similar to that of foreign clinical studies in Europe and America, and no unexpected new safety signal is reported, it is further confirmed that ATG-008 is well tolerated and further dose escalation is allowed.

- **Clinical PK: the PK profile of this study was similar to the PK profile of foreign patients in Europe and America**

The foreign study (Europe and America) CC-223-ST-001-Part A demonstrated that the unchanged ATG-008 showed linear relationship within the dose range of 7.5 mg~60 mg, and the exposure level of metabolite M1 also presented linear relationship with the dose.

The preliminary PK results of this study (ATG-008 15 mg and 30 mg) showed that the exposure level of active compound and its metabolite presented linear relationship with the dose. Compared with PK parameters of foreign studies in Europe and America, the active compound had numerically higher C_{max} and shorter T_{max}. The active compound and its metabolite had similar elimination rate (in different dose groups). Analysis of difference in PK parameters in Europe, America, and Asia showed that the difference in exposure level mainly caused by C_{max} difference, which might be related to lighter body weight and smaller volume of distribution of Asian patients.

According to the currently available data, it was estimated that the exposure level of 20 mg/BID might be lower than that of 45 mg/QD, supporting that the administration mode BID could be explored in this study. According to the above clinical efficacy, safety and PK study results, the sponsor proposed to add 2 dose groups, i.e., 45 mg/QD and 20 mg/BID (approximately 20 subjects

each), to further explore and evaluate the PK, safety, tolerability and efficacy of ATG-008 in advanced HBV+ HCC subjects.

Length of Trial

The first part of this study had enrolled 35 subjects.

According to the previous study results, the sponsor proposes to continue to enroll approximately 40 subjects. Approximately 6 months are needed for enrollment period. Completing PK (PK samples will be collected from 10 subjects each in the two dose groups), safety and preliminary efficacy evaluations is expected to take approximately 6 months.

The end of Study is defined as either the date of the last visit of the last subject to complete the trial, or the date of receipt of the last data point (e.g., date of death) from the last subject that is required for primary analysis, whichever is the earlier date.

Study Treatments

The starting dose of ATG-008 will be 15 mg daily for 28 days each cycle for the first 6 fully evaluable (including PK outcomes) subjects. Providing dose-limiting toxicity (DLT) occur in less than 2 of 6 subjects who complete Cycle 1, additional 24 subjects will be enrolled at the starting dose of 30 mg daily. Subjects who tolerated the 15-mg dose level, may then dose-escalate to 30 mg at the Investigator's discretion until enrollment of 30-mg group starts.

According to the previous study results, the sponsor plans to continue to enroll approximately 40 subjects with hepatitis B virus (HBV) positive, unresectable HCC subjects who have previously received at least one prior line of systemic therapy. Among which, approximately 20 subjects will receive oral ATG-008 at an initial dose of 45 mg/QD and another 20 subjects will receive oral ATG-008 at an initial dose of 20 mg/BID.

If the overall response rate (ORR) of tumor is greater than 15% in the study dose group (45 mg/QD or 20 mg/BID), then this study will be expanded to enroll additional approximately 110 subjects using ORR as the primary study endpoint, to further evaluate the efficacy and safety of ATG-008.

The subjects enrolled will be treated with ATG-008 at an initial dose of 45 mg/QD or 20 mg/BID in continuous 28-day cycles (except cycle 1) until the appearance of radiologic disease progression, toxicity, subject or physician decision or death. At the discretion of the Investigator, treatment may continue beyond radiologic progression until clear symptomatic deterioration if no other treatment options are available.

Continuous dose interruption of up to 2 weeks and the total discontinuation time not more than 4 weeks is allowed in this study. Dose reduction principle: 30 mg/QD can be reduced to 20 mg/QD and 15 mg/QD; 45 mg/QD can be reduced to 30 mg, 20 mg, 15 mg/QD; 20 mg/BID can be reduced to 15 mg/BID or other doses to mitigate toxicity. If further dose reduction is required, it can be implemented according to the considerations of the investigator and discussion between the investigator and medical monitors of the sponsor. Dose re-escalation (higher than the initial dose is not permitted) will be allowed if the same toxicity does not recur at the reduced dose for least one cycle (4 weeks).

Antiviral therapy is required, and HBV-DNA viral load will be monitored in all subjects with chronic HBV infection. Serum AST/ALT is also monitored.

After cessation of study drug treatment, subsequent anti-cancer therapy and survival status will be followed in all subjects until death.

Overview of Efficacy Assessments

Subjects will be evaluated for tumor response and progression according to RECIST 1.1 guidelines every 8 weeks (± 5 days) until radiologic disease progression, death or withdrawal of consent. mRECIST may be also used when the trial is expanded, if necessary.

All anticancer treatments administered, especially for HCC, following the last dose of study drugs will be captured until death or withdrawal of consent. Disease progression and date of progression on each subsequent therapy will be documented. Following disease progression, survival will be followed every 8 weeks (± 1 week) until death or withdrawal of consent.

Overview of Safety Assessments

All subjects will be monitored for adverse events, starting from the time the subject signs the informed consent form (ICF) until 28 days after the last dose of study drug. A thorough evaluation of medical conditions will be conducted during screening for eligibility. Vital signs, laboratory assessments (e.g. serum chemistry, hematology, fasting plasma glucose, glycated hemoglobin [HbA1c]), 12-lead electrocardiogram (ECGs), and ECOG performance status will be monitored. Contraception must be practised during the trial to avoid pregnancy in trial subjects and their partners, and females of child-bearing potential will have regular pregnancy testing.

Overview of Pharmacokinetic Assessments

Blood samples will be collected for intensive sampling in all 30 subjects in order to estimate the PK of ATG-008 and metabolites in Asian subjects.

As for the 2 dose groups 45 mg/QD and 20 mg/BID, PK samples of 10 subjects each should be collected to further evaluate the PK profile of ATG-008 and its metabolites.

Overview of Exposure-Response Analyses

Exposure-response analyses will be performed to evaluate relationships between ATG-008 and/or M1 exposure and clinical outcomes of efficacy and safety.

Statistical Summary

The primary efficacy endpoint is ORR, and the primary analysis population for both efficacy and safety analysis is the Treated population.

All efficacy and safety results will be tabulated and/or summarized using for the Treated population by treatment arm.

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Table 1: List of Abbreviations

Abbreviation	Term
AASLD	American Association for the Study of Liver Disease
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AFP	Alpha-fetoprotein
AKT	Serine/threonine kinase
ALT (SGPT)	Alanine amino transferase
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate amino transferase
ATG-008	Formerly CC-223, a dual mTOR kinase inhibitor
BCLC	Barcelona Clinic liver cancer
BCRP	Human breast cancer resistance protein
BSC	Best supportive care
BUN	Blood urea nitrogen
CBC	Complete blood count
CC-223	Former (US) code name for ATG-008, a dual mTOR kinase inhibitor
CK	Creatinine kinase
CL/F	Clearance as a function of bioavailability
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTPM	Clinical trials planning meeting
CYP	Cytochrome P
DCR	Disease control rate
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
EASL	European Association for the Study of Liver
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGF	Endothelial growth factor
EGFR	Epidermal growth factor

Abbreviation	Term
ERK	Extracellular signal-regulated kinase
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of treatment
EU	European Union
FACT	Functional Assessment of Cancer Therapy
FCBP	Females of child bearing potential
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
fT4	Index of free thyroxin
GCP	Good clinical practice
G-CSF	Granulocyte colony stimulating factor
GI	Gastrointestinal
GM-CSF	Granulocyte macrophage colony stimulating factor
HbA1c	Hemoglobin A1c
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HER3	Human epidermal growth factor 3
hERG	Human ether-à-go-go-related gene
HNSTD	Highest nonseverely toxic dose
HR	Hazard ratio
IA	Interim analysis
IC50	50% inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IGF	Insulin like growth factor
INR	International normalized ratio
IP	Investigational product
IRS1	Insulin receptor substrate 1
LDH	Lactate dehydrogenase
M1	Major human metabolite of ATG-008
MedDRA	Medical Dictionary for Regulatory Affairs

Abbreviation	Term
mm	Millimeter
MRI	Magnetic resonance imaging
mRECIST	Modified Response EvaluationCcriteria in Solid Tumors
mRNA	Messenger ribonucleic acid
MRCT	Multi-regional clinical trial
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NET	Neuroendocrine tumor
NSCLC	Non-small cell lung cancer
OAT	Organic anion transporter
OCT	Organic cation transporter
ORR	Overall response rate
OS	Overall survival
pAKT	Phosphorylated AKT
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PI	Principal Investigator
PI3K	Phosphoinositide 3-kinase
PK	Pharmocokinetic
PR	Partial response
PT	Prothrombin time
PTEN	Phosphatase and tensin homolog
PTT	Partial thromboplastin time
QD	Once daily
QLQ	Quality of life questionnaire
QTcF	Fridericia correction
RBC	Red blood cell
RECIST 1.1	Response Evaluation Criteria in Solid Tumors 1.1
RFA	Radiofrequency ablation
RR	Response rate

Abbreviation	Term
SAE	Serious adverse event
SC	Steering committee
SD	Stable disease
SOP	Standard operating procedure(s)
STD10	Severely toxic dose in 10%
SUSAR	Suspected unexpected serious adverse reaction(s)
SUV	Standardized uptake value
TACE	Transcatheter arterial chemoembolization
TEAE	Treatment emergent adverse event
TSH	Thyroid stimulating hormone
TTP	Time to progression
ULN	Upper limit of normal
US	United States of America
Vd/F	Volume of distribution as a function of bioavailability
VEGF	Vascular endothelial growth factor
WBC	White blood cell

1. INTRODUCTION

1.1. Hepatocellular Carcinoma

Hepatocellular carcinoma represents up to 90% of all primary liver cancers in the world (Hashim, 2016; Torre, 2016). Liver cancer ranks in incidence and mortality among the top 10 cancers worldwide. It is the fifth most common cancer in men and the ninth most common cancer in women, with 554,000 new cases in men and 228,000 in women worldwide in 2012. It is the second most common cause of death from cancer, estimated to be responsible for nearly 745,000 deaths in 2012 (9.1% of the total cancer mortality) (Ferlay, 2015).

HCC shows great geographical variation with a high incidence in Asia and Sub-Saharan Africa and a rising incidence in the United States of America (US) and Europe (Parkin, 2005; El Serag, 1999; Zhu, 2016). Hepatitis C virus (HCV) infection is the predominant risk factor for HCC in Western countries and Japan, whereas HBV is the predominant risk factor for HCC in Southeast Asia and Africa. Chronic HBV infection now accounts for 80% of all newly diagnosed HCC in Asia (Zhu, 2016). More than 50% of new cases and deaths occur in China (Parkin, 2005) where it is the second most common cancer (Yang, 2005a), and 80-90% of cases are caused by chronic infection with hepatitis B (Raza, 2007).

It is expected that hepatitis B vaccine will eventually reduce the incidence of HCC. Many countries now offer hepatitis B vaccination of all newborns. However, three or four decades will be needed to assess the real impact of hepatitis B virus control on HCC incidence because diagnosis of hepatitis-related HCC occurs at a mean age of 55-60 years (Lau, 2008).

HCC is diagnosed based on pathology or radiology. Pathological diagnosis is generally based on immunostaining for GPC3, HSP70, and glutamine synthetase and/or gene expression profiles (GPC3, LYVE1, and survivin) to differentiate high grade dysplastic nodules from early HCC. In addition, classic radiologic features have been used in clinical practice to make the diagnosis of HCC. Guidelines for HCC diagnosis have been developed by the European Association for the Study of Liver (EASL) and European Organization for Research and Treatment of Cancer (EORTC) (Llovet, 2012b) and American Association for the study of Liver Disease (AASLD) (Bruix, 2010). Specifically, the AASLD guidelines stipulate that HCC can be diagnosed either by pathology or radiology meeting the following criteria:

- ☐ Dynamic imaging obtained by 4-phase multidetector CT scan or dynamic contrast-enhanced MRI
- ☐ Arterial hypervascularity was present
- ☐ Venous-delayed phase washout was present.

An expert panel has considered these non-invasive criteria as acceptable to be used as entry criteria in clinical trials of HCC (Llovet, 2008b).

Among several available classification systems for HCC, the Barcelona Clinic Liver Cancer (BCLC) classification has emerged as the standard and has been recommended for use in trial design and clinical management of HCC (Llovet, 2008a). According to the BCLC staging classification and treatment schedule, patients with very early stage HCC (Stage 0) and early stage HCC (Stage A) are candidates for radical therapy (resection, liver transplantation, or local ablation via percutaneous ethanol injection or radiofrequency ablation). Patients with intermediate stage HCC (Stage B) may benefit from transarterial chemoembolization. Patients with advanced stage HCC (Stage C) benefit from sorafenib. Patients with end-stage HCC (Stage D) receive symptomatic treatment (see Section 19.4.1).

The prognosis for HCC remains very poor despite advances in diagnostic technology and

treatment. Five-year survival rates for advanced stage disease are only 3% to 5% worldwide (Parkin, 2005). Potentially curative treatments are applied to only 30% to 40% of patients in developed countries (Llovet, 2003). The risk of recurrence is approximately 70% at 5 years after resection and prognosis after recurrence is poor (Llovet, 2003). Patients with HCC of Stage B and C have a median survival ranging from 10 to 14 months following appropriate treatments.

To date, sorafenib at a dose of 400 mg twice-daily is the only first-line systemic therapy proven to prolong overall survival (OS) in subjects with advanced HCC. One phase 3 trial (SHARP) conducted in Europe, North America, South America and Australia showed that sorafenib as first-line therapy improved OS compared with placebo (10.7 months versus 7.9 months, Hazard Ratio (HR)=0.69, 95%CI, 0.55-0.87; p<0.001) (Llovet, 2008b). A second trial conducted in Asia (ORIENTAL) with similar design confirmed the survival benefit of sorafenib although Asian subjects had a poorer overall outcome (6.5 months versus 4.2 months, HR=0.68, 95%CI, 0.50-0.93; p=0.014) (Cheng, 2009). Three recent phase 3 trials of other therapeutic agents performed in advanced stage HCC in the first-line setting have failed to demonstrate a survival benefit, or even non-inferiority, over single agent sorafenib. These included two single-agent trials of the multi-targeted kinase inhibitors, brivanib and linifanib, and a combination trial of erlotinib (an epidermal growth factor [EGFR] inhibitor) plus sorafenib (Johnson, 2013; Cainap, 2015; Zhu, 2015).

Systemic chemotherapy was usually used as a palliative treatment. However, a phase 3 trial (EACH) revealed a possible beneficial role for FOLFOX4 (fluorouracil, leucovorin and oxaliplatin) in China and other Asian countries (Qin, 2013). This trial evaluated 371 subjects with HCC in China, Taiwan, Korea and Thailand and randomized them (1:1) to either FOLFOX4 or doxorubicin. FOLFOX4 showed significant improvement in progression-free survival (PFS) (2.93 months versus 1.77 months, HR=0.62, 95% CI, 0.49-0.79, p<0.001), RR (67% versus 8.15%, p =0.02), DCR (52.17% versus 31.55%, P < 0.0001) than for those treated with doxorubicin. No improvement was found in median OS (6.40 months versus 4.97 months, HR=0.80, 95% CI, 0.63-1.02, P=0.07) but a further follow-up of 7 months showed a beneficial effect of mOS in FOLFOX4 group (6.47 months versus 4.90 months, p = 0.04). The oxaliplatin-containing FOLFOX4 regimen for treatment of advanced HCC was subsequently approved by the Chinese Food and Drug Administration (CFDA) in 2013.

The pursuit for second-line therapy has not identified any very promising new treatment options for HCC. Results of a second-line trial of brivanib versus placebo (randomized 2:1) in 395 subjects with advanced HCC who progressed on or were intolerant to sorafenib failed to demonstrate improvement in OS (9.4 versus 8.2 months, HR 0.89, p = 0.33) (Llovet, 2012a). Secondary endpoints showed an improvement with brivanib, including time to progression (TTP) (4.2 versus 2.7 months, HR=0.56, p=0.0001), disease control rate (71% versus 49%, p<0.0001) and overall tumor response rate (12% versus 2%, p=0.003). The failure of this trial was attributed at least partially to an imbalance in baseline prognostic factors, including the frequency of macrovessel invasion and alpha-fetoprotein (AFP) levels, both of which were higher in the brivanib arm. Subjects were stratified by study site, ECOG performance status, sorafenib outcome, and vascular invasion/extrahepatic spread. Results demonstrated tumor responses in 3% to 4% of subjects with a median time to progression of 3 to 4 months.

No effective second-line therapy existed for sorafenib failures until the approval of regorafenib by the US FDA in 2017 following results of a randomised, double-blind, parallel-group, phase 3 trial (RESOURCE) in the second-line setting (Bruix, 2017). The trial enrolled 573 HCC subjects who progressed on sorafenib and randomised them (2:1) to either regorafenib (n=379) or placebo (n=194). Regorafenib improved median OS (10.6 months versus 7.8 months, HR=0.63, 95% CI, 0.50-0.79; one-sided p<0.0001), median PFS (3.1 months versus 1.5 months, p<0.0001) and TTP

(3.2 months versus 1.5 months, p<0.0001) compared with placebo.

Even today, treatment options for unresectable stage HCC are severely limited. There remains a high unmet medical need for effective therapies in this disease, particularly in Asian HBV+ HCC subjects failing at least one prior line of systemic therapy.

1.2. Mammalian Target of Rapamycin

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase related to the lipid kinases of the phosphoinositide 3-kinase (PI3K) family. It functions as a sensor of mitogen, energy and nutrient levels and is a central controller of cell growth. mTOR exists in 2 complexes: mTORC1, which complexes with raptor and is rapamycin sensitive, and mTORC2, which complexes with rictor and is rapamycin insensitive (Kim, 2002; Sarbassov, 2004). mTORC1 integrates signals from growth factor receptors with cellular nutritional status and controls the level of messenger ribonucleic acid (mRNA) translation by modulating the activity of key translational components. The functions of mTORC2 are less well understood than those of mTORC1 (Feldman, 2009). mTORC2 is thought to modulate growth factor signaling by phosphorylating kinases such as AKT (a serine/threonine kinase), which leads to its activation. Active AKT promotes cell survival in many ways, including suppressing apoptosis, promoting glucose uptake, and modifying cellular metabolism (Gibbons, 2009). The PI3K–AKT pathway is inappropriately activated in many cancers and is vital to the growth and survival of cancer cells (Engelman, 2009). Therefore, mTOR inhibitors are being developed as potential therapeutic agents for the treatment of various cancers. Rapamycin and its analogues inhibit the mTORC1 complex alone and stimulate the upstream kinase AKT by inhibiting the negative feedback loop between p70S6 kinase and insulin receptor substrate 1 (IRS1). This may explain, at least in part, the resistance to rapamycin analogues exhibited by the majority of cancer cell lines and tumors (Gibbons, 2009). The inhibition of both mTORC1 and mTORC2 by mTOR kinase inhibitors would therefore be expected to inhibit AKT instead of activating it.

1.2.1. Hepatocellular Carcinoma and mTOR

Activation of several signaling pathways have been implicated in human hepatocarcinogenesis. These include pathways involved in cell proliferation (PI3K/mTOR, EGFR, IGF1R, Met), liver development and cell differentiation (Wnt and Hedgehog), inflammation and angiogenesis (Villanueva, 2008b).

The PI3K/AKT/mTOR pathway is an important signaling pathway driving cell growth and proliferation in HCC. Loss of phosphatase and tensin homolog (PTEN) expression, often due to promoter hypermethylation, is a common aberration present in 30% – 50% of HCC and is associated with mTOR pathway activation, vascular endothelial growth factor (VEGF) activation and a more aggressive phenotype (Yang, 2005b; Mi, 2006; and Hayashi, 2009).

Analysis of 314 HCC samples for genetic alterations and protein expression levels showed activation of insulin-like growth factor (IGF) pathway, overexpression of endothelial growth factor (EGF), loss of PTEN, and activation of mTOR signaling in 50% of the samples. Rictor copy number gain, also associated with mTOR pathway activation, was observed in 25% of HCC. TORC2 pathway activation, associated with increased expression of phosphorylated AKT (pAKT), is observed in the majority of HCC and is associated with vascular invasion, high tumor stage and grade, and a poor prognosis (Villanueva, 2008a).

Rapamycin has been shown to inhibit HCC cell-line proliferation in vitro, and tumor growth and angiogenesis in vivo (Semela, 2007). Similar results have been observed with the rapamycin analogue, everolimus, in xenograft models (Huynh, 2009; Villanueva, 2008a). These studies provide a strong rationale for clinical investigation of mTOR pathway inhibitors in subjects with

HCC and for compounds with inhibitory activity against both TORC1 and TORC2 complexes.

Although the mechanisms mediating sorafenib resistance have not been completely characterized, preclinical studies suggest that activation of EGFR, STAT3 and PI3K/AKT signaling are involved. Hepatocellular carcinoma cell lines with acquired sorafenib resistance exhibit increased levels of pAKT and p85 (a PI3K regulatory subunit) and down-regulation of PTEN, consistent with activation of the mTOR pathway. Furthermore, treatment of resistant cells with an allosteric AKT inhibitor restored sensitivity of resistant cells to sorafenib induced apoptosis (Chen, 2012). In a separate study, HCC cells with acquired resistance to sorafenib were shown to have aberrant activation of EGFR/human epidermal growth factor 3 (HER3) receptors as well as over-expression of several EGFR ligands. These enhanced autocrine/paracrine loops led to the constitutive activation of extracellular signal-regulated kinase (ERK) and AKT and conferred increased sensitivity to gefitinib (Blivet-Van Eggepoël, 2012).

These data provide additional support for treatment of HCC following progression on sorafenib with mTOR targeted therapies that inhibit both TORC1 and TORC2 complexes, thereby blocking pAKT activation.

1.3. ATG-008

ATG-008 (formerly CC-223, CC0482223) is a potent and selective inhibitor of the mTOR kinase in development for the treatment of solid and hematologic malignancies. It is a dual inhibitor of both the mTORC1 and mTORC2 complexes, which is hoped may minimize development of resistance due to increased phosphorylation of AKT.

1.3.1. ATG-008 Preclinical Data

ATG-008 was screened against a panel of 138 cancer cell lines (40 hematological, 43 breast, 2 colorectal, 7 endometrial, 1 glioma, 11 HCC, 1 melanoma, 27 non-small cell lung, 5 ovarian, and 1 prostate cancer). In the majority of cell lines, ATG-008 treatment resulted in concentration-dependent growth inhibitory activity. ATG-008 inhibited the mTOR pathway in multiple cell lines, as evidenced by inhibition of both direct (4EBP1 and AKT Ser473) and indirect (S6RP, PRAS40, GSK3β) substrates of the 2 complexes mTORC1 and mTORC2 that contain the mTOR kinase.

ATG-008 has demonstrated potent antiproliferative activity in a panel of 11 HCC cell lines in vitro, with activity greater than either sorafenib or erlotinib. The two most sensitive cell lines have Rictor copy number gain. Synergistic antiproliferative activity with the combination of ATG-008 and sorafenib was observed across multiple cell lines and a synergistic effect of the combination on inhibition of anchorage independent cell growth was observed in HepG2, but not SK-Hep1 HCC cells.

Characterization of the in vivo antitumor activity of ATG-008 in xenograft models has focused on PC3 human prostate, U87MG glioblastoma and HCT-116 colorectal tumors. ATG-008 significantly inhibited PC3, U87MG, and HCT-116 tumor growth in a dose- and schedule-dependent manner. The minimum dose required to obtain approximately 65% tumor volume reduction compared with vehicle control was 5 mg/kg dosed twice daily, 1 mg/kg dosed once daily, and 25 mg/kg dosed once daily for PC3, U87MG and HCT-116 tumors, respectively. In addition, ATG-008 also caused regression of larger (464 mm^3) PC3 tumors. The antitumor effect of ATG-008 in PC3 and U87MG tumors was not only due to the inhibition of tumor cell proliferation but also due to increased apoptosis and antiangiogenic activity. In PC3, U87MG, and HCT-116 tumor-bearing mice treated with ATG-008, significant inhibition of mTOR pathway markers S6RP and AKT Ser473 was observed following a single oral dose or multiple doses, indicating that the antitumor activity was mediated through the inhibition of both mTORC1

(S6RP) and mTORC2 (AKT Ser473). In PC3 tumors, the pharmacokinetic (PK)/pharmacodynamic relationship of compound exposure and biomarker response indicated that > 80% inhibition of phosphorylated S6 ribosomal protein (pS6RP) and > 60% inhibition of pAKT at serine 473 (pAKT Ser473) were obtained at total drug plasma concentrations greater than 0.2 M. Maintenance of plasma levels > 0.2 M and this degree of biomarker inhibition through 8 hours twice daily confers good antitumor activity in PC3 tumors. The combinatorial effects of ATG-008 and sorafenib were tested in a human HCC orthotopic xenograft model. Both agents demonstrated single agent activity, and a synergistic inhibitory effect on tumor growth.

CC0483131 (O-desmethyl-ATG-008), the major human metabolite of ATG-008 (M1), has antiproliferative activity in vitro, inhibited mTOR pathway biomarkers in vitro and in vivo, and exhibited antitumor activity. These data suggest that the presence of the M1 metabolite could contribute to the therapeutic activity of ATG-008 in subjects.

In vitro and in vivo preclinical studies have been conducted to characterize the absorption, distribution, metabolism and excretion (ADME) of ATG-008. The results demonstrate that ATG-008 has acceptable ADME profiles. In vitro plasma protein binding is moderate (92.4%) for CC- 223 and high (98.1%) for the major metabolite M1 (O-desmethyl-ATG-008), and was concentration-independent. In a quantitative whole body autoradiography study, drug-derived radioactivity was widely distributed in rat tissues after oral administration, and elimination from tissues was nearly complete at 168 hours post-dose. The fecal route was the major excretion pathway, while biliary excretion and urinary clearance also contributed to the elimination of [^{14}C] ATG-008-derived radioactivity in rats and dogs. Formation of M1 (CC0483131) was the major metabolic pathway in humans, mediated by cytochrome P450 (CYP)3A4/5, with a minor contribution from CYP2C9. Oxidative metabolism of M1 in human liver microsomes was slow, mediated by CYP2C8 and CYP3A4/5 and glucuronidation of M1 is a minor pathway mediated by UGT1A8. In vitro CYP inhibition studies demonstrate that ATG-008 is a weak inhibitor of CYP2C9 and CYP2C19 (50% inhibitory concentration [IC_{50}] ≥ 27.4 µM) and is not expected to precipitate clinically relevant drug-drug interactions at projected therapeutic concentrations due to the inhibition of the metabolism of co-administered substrates of these enzymes. In human hepatocyte cultures, ATG-008 (1 to 10 µM) treatment for two days did not induce the catalytic activities or messenger ribonucleic acid (mRNA) levels of CYP1A2 and CYP2B6 to a notable extent. ATG-008 increased CYP3A4 mRNA expression to a variable extent (approximately 1% to 64% of the response observed with the positive control rifampicin), but did not induce the catalytic activity of CYP3A4/5 to a notable extent. ATG-008 metabolite M1 is a weak inhibitor of CYP2C9 and CYP2C19, with estimated IC_{50} values of 63 µM and 46 µM, respectively. M1 is not a time-dependent inhibitor of the CYP enzymes. In human hepatocyte cultures, M1 (5 to 50 µM) treatment for two consecutive days did not induce the catalytic activities of CYP1A2, CYP2B6 and CYP3A4/5 to a notable extent. M1 treatment did not increase the mRNA level of CYP1A2, but increased CYP2B6 mRNA expression up to an average of 12.4% of the response observed with the positive control phenobarbital, and CYP3A4 mRNA expression up to an average of 34.8% of the response observed with the positive control rifampicin. ATG-008 is not a substrate but is an inhibitor (IC_{50} = 3.67 µM) of human p-glycoprotein. ATG-008 is a substrate and an inhibitor (IC_{50} = 11.7 µM) of human breast cancer resistance protein (BCRP). At a clinically relevant concentration of 1 µM, ATG-008 did not show any notable inhibition of organic anion transporter 1 (OAT1), OAT3, OATP1B1, OATP1B3, or organic cation transporter 2 (OCT2) transportability in vitro. ATG-008 metabolite M1 is a substrate and a weak inhibitor of P-gp. M1 is also a substrate and an inhibitor of BCRP.

ATG-008 was evaluated in a core battery of safety pharmacology studies (neurobehavior, respiratory and cardiovascular) as well as the human ether-à-go-go-related gene (hERG) assay

and mutagenesis assay. ATG-008 had no effects on central nervous system (CNS) function in rats at single doses up to 10 mg/kg. In a rat respiratory study, there were no adverse effects on respiration observed in a 28-day repeat-dose study. There was minimal inhibition in the hERG assay (IC_{50} = 112 µM). The M1 metabolite demonstrated minimal inhibition (IC_{50} > 100 µM) in the in vitro hERG assay. In an assessment of cardiovascular function in dogs, a small decrease in heart rate and a concomitant prolongation in R Wave to R Wave (RR) interval were observed 1-hour postdose at 3 mg/kg but were not considered significant.

ATG-008 was negative in the microbial mutagenesis assays, the in vitro assay for chromosomal aberrations in human peripheral blood lymphocytes, and the in vivo rat bone marrow micronucleus assay.

The potential toxicity of ATG-008 has been characterized in pivotal good laboratory practice repeat-dose toxicity studies of 28 days in duration with a 28-day recovery period in rats and dogs.

In the definitive 28-day oral toxicity studies, doses were 0.75, 1.5, 3 and 10 mg/kg/day in dogs and 1, 3 and 10 mg/kg/day in rats. A 28-day drug-free recovery period was included at the end of the dosing period in each study. The primary target organs of toxicity after 28 days of repeated administration in rats and in dogs were similar and included the gastrointestinal tract (acute inflammation), bone marrow (hypocellularity) and lymphoid tissues (lymphoid depletion in peripheral lymph nodes, thymus, spleen and/or Peyer's patches). In exploratory studies, modulation of insulin and glucose was observed in rats and dogs, consistent with the pharmacology of mTOR inhibitors.

In rats, the severely toxic dose in 10% of animals tested (STD10) was 10 mg/kg/day, and in dogs, 1.5 mg/kg/day was established as the highest nonseverely toxic dose (HNSTD). Systemic exposures in rats at 3 and 10 mg/kg/day (10595 and 45 ng•hr/mL, respectively) are approximately 9- and 38-fold higher than human exposure at 30 mg/day (1202 ng•hr/mL).

Exposure in dogs at the HNSTD of 1.5 mg/kg/day is approximately 2-fold greater than human exposure at 30 mg/day. The M1 metabolite was observed in the plasma of rats and dogs but at levels lower than those that occur in humans (data on file).

1.3.2. ATG-008 Clinical Data

To date, five clinical studies with ATG-008 have been completed and one other is ongoing. Three clinical pharmacology studies (CC-223-CP-001, CC-223-CP-002, and CC-223-CP-003) involved 50 healthy subjects. Study CC-223-ST-001 and CC-223-NSCL-001, and ongoing CC-223-DLBCL-001, enrolled 402 subjects with various solid and hematologic malignancies. Details were listed below.

CC-223-CP-001 (Formulation study: Tablet vs API in capsule)

CC-223-CP-002 (ADME and food effect study)

CC-223-CP-003 (Drug-drug interaction study)

CC-223-ST-001 (First in human dose escalation and expansion study in multiple tumor types)

CC-223-NSCL-001 (Combination study in NSCL)

CC-223-DLBCL-001 (Combination study in DLBCL)

In Study CC-223-CP-001, 18 healthy adult male subjects were administered a single 20-mg ATG-008 capsule, four 5-mg ATG-008 tablets, and a single 20-mg tablet with a 7-day interdose washout between each treatment. The 20 mg ATG-008 capsules, 5 mg ATG-008 tablets, and 20-mg ATG-008 tablets had comparable ATG-008 exposure indicating comparable bioavailability. ATG-008 is rapidly absorbed with mean peak concentrations of ATG-008 and M1 generally observed within 1 to 3 hours. The mean terminal half-lives for ATG-008 and M1

were approximately 6 and 14 hours, respectively.

Study CC-223-CP-002 was conducted in 18 healthy adult male subjects (6 subjects in Part 1 and 12 subjects in Part 2). Subjects in Part 1 received a single 20-mg oral dose of ATG-008 capsule containing a microtracer of [^{14}C]ATG-008 solution. Subjects in Part 2 received a single oral 20-mg dose of ATG-008 under fed or fasted conditions. ATG-008 was well absorbed systemically, as reflected by unchanged ATG-008, accounting for less than 2% of the administered dose recovered in urine and feces combined. ATG-008 represented approximately 16% of circulating TRA exposure. ATG-008 was extensively metabolized to 7 metabolites measured in urine and feces: M1, M2, M4, M7, M8, M11, and M13. Of these 7 metabolites, only M1, M2, and M13 were measurable in plasma. M1 was formed via odemethylation and was the primary circulating entity in plasma representing approximately 77% of circulating TRA exposure. Renal elimination was the primary excretion route for TRA. ATG-008 and M1 exposure were not markedly changed in healthy adult males administered a single, 20-mg oral dose of ATG-008 with or without consuming a high, fat meal. Tmax was delayed 1 and 3 hours for ATG-008 and M1, respectively, after ATG-008 was administered with a meal. These differences are expected to have minimal clinical impact.

In Study CC-223-CP-003, 14 healthy adult male subjects received ketoconazole (a strong CYP3A4 inhibitor) co-administered with a single 20 mg dose of ATG-008. After coadministration with ketoconazole (400 mg), a strong CYP3A4 inhibitor, there were moderate increases by approximately 60% and 70% increase in ATG-008 and M1 exposure, respectively, following a single 20 mg dose of ATG-008. The moderate increase was much less than the pronounced increase (>3-fold) observed in the CYP3A4 inhibition assay in vitro, suggesting a compensatory non-CYP3A4 mediated metabolism/elimination pathway, moderated the inhibited CYP3A4 activity on overall ATG-008 metabolism and elimination. These findings may be extrapolated to coadministration of ATG-008 with other moderate to strong CYP3A4 inhibitors, the resultant moderate increase in ATG-008 exposure supports clinical management rather than prospective dose adjustment of ATG-008.

The first-in-human, phase 1/2 dose escalation and expansion clinical study (CC-223-ST-001) to assess the safety, tolerability, PK and preliminary efficacy of ATG-008 in subjects with solid tumors and hematologic malignancies, was completed in November 2016. During the dose escalation phase (phase 1), 28 subjects were treated with continuous once daily (QD) dosing across 5 dose levels: 7.5 mg (n=1), 15 mg (n=2), 30 mg (n=9), 45 mg (n=9) and 60 mg (n=7). The dose of 45 mg QD was selected for the expansion phase (phase 2) of this study which was conducted in 198 subjects across 7 tumor types including HCC, non-small cell lung cancer (NSCLC), glioblastoma multiforme (GBM), hormone receptor positive breast cancer (HRPBC), neuroendocrine tumor (NET) of non-pancreatic origin, diffuse large B-cell lymphoma (DLBCL) and multiple myeloma (MM). CC-223-ST-001 is the sole study evaluating HCC subjects to date.

Study CC-223-NSCL-001 evaluated the safety, tolerability, and PK of single- and multiple-ascending doses of CC-223 combined with either erlotinib or CC-486 (oral azacytidine) in subjects with advanced NSCLC and who had failed at least one line of standard therapy. It was a phase 1b dose escalation and expansion study evaluating escalating doses of CC-223 in combination with 2 doses of erlotinib administered concurrently with CC-223 (Arm A) or 2 doses of CC-486 administered either concurrently with CC-223 (Arm B) or sequentially with CC-223 (Arm C), followed by expansion of one or more combination cohorts at one or more selected doses. This study was terminated early, during the dose-finding phase, due to the changing landscape in NSCLC treatment and changes in the sponsor's overall strategy and portfolio management. The study was not terminated because of any specific safety concerns.

Study CC-122-DLBCL-001 (ongoing) is evaluating CC-223 as part of novel combinations with CC-122 and CC-292 administered as doublets, and as triplets in combination with rituximab, in subjects with relapsed or refractory DLBCL. As of the 2 May 2016 data cutoff date, a total of 102 subjects were enrolled into the ongoing dose escalation phase of the study.

1.3.2.1 CC-223-ST-001 Efficacy in Hepatocellular Carcinoma

In phase 2 of the CC-223-ST-001 study, 53 subjects with HCC received at least 1 dose of ATG-008 (CC-223). Overall, 41 (77.4%) were included in the efficacy-evaluable (EE) population. Twelve (22.6%) subjects, including 8 Asian, were considered HBV+ and 41 (77.4%) were HBV-.White was the major race (30 of 41). The majority (48 of 53, 90.6%) of subjects with HCC had received prior sorafenib treatment, including 100% (8 of 8) of HBV+ Asian subgroup. A total of 15% subjects had received chemotherapy including cisplatin, oxaliplatin or doxorubicin; 17% had received both sorafenib and chemotherapy.

The initial ATG-008 starting dose (n=25) was 45 mg/QD but later subjects (n=28) started treatment at 30 mg/day because of frequent dose modifications required to mitigate toxicity. For the whole population, the median OS (mOS) was 30.0 weeks (95% CI: 20.9, 61.1). The mOS in the 30-mg and 45-mg dose groups was 38.9 weeks (95% CI: 19.6, 63.3) and 25.0 weeks (95% CI: 15.0, not estimable), respectively (Table 2). The difference between the dose groups was not statistically significant. The mOS in the HBV+ and HBV- subgroups was 52.4 weeks (95% CI: 25.6, 89.1) and 22.4 weeks (95% CI: 15.4, 50.1), respectively. OS for HBV+ subjects was more favorable than for HBV- subjects, but the difference was not statistically significant (p = 0.1897).

The objective response rate (ORR) (complete response [CR] + partial response [PR]) was 5.7% (95% CI: 1.2%, 15.7%). By HBV status, the ORR was 25.0% (95% CI: 5.5%, 57.2%) for subjects who were HBV+ and 0% for those who were HBV-. Overall, no subject had a CR; 3 (5.7%) subjects had a best response of PR (all 3 subjects were HBV+, 2 of them were treated with 45mg/QD); and 26 (49.1%) subjects had a best response of stable disease (SD) (8 [66.7%] HBV+ subjects and 18 [43.9%] HBV- subjects). Six (11.3%) subjects had a best overall response of progressive disease (PD) (1 [8.3%] HBV+ subject and 5 [12.2%] HBV- subjects).

The DCR for all subjects was 54.7% (95% CI: 40.4%, 68.4%). By HBV status, the DCR was 91.7% (95% CI: 61.5%, 99.8%) for subjects who were HBV+ and 43.9% (95% CI: 28.5%, 60.3%) for those who were HBV-.

The rate of target tumor shrinkage (ie, lesions reducing in size relative to screening) for all subjects was 45.3% (95% CI: 31.6%, 59.6%). By HBV status, the target tumor shrinkage rate was 66.7% (95% CI: 34.9%, 90.1%) for subjects who were HBV+ and 39.0% (95% CI: 24.2%, 55.5%) for those who were HBV-.

Table 2: Overall Survival for HCC by Starting Dose and by HBV Status in Phase 2 of Study CC-223-ST-001 (Treated Population)

	HCC				
	Overall (N=53)	**30 mg/day (N=28)**	**45 mg/day (N=25)**	**HBV+ (N=12)**	**HBV- (N=41)**
Death, n (%)	33 (62.3)	23 (82.1)	10 (40.0)	7 (58.3)	26 (63.4)
Censored, n (%)	20 (37.7)	5 (17.9)	15 (60.0)	5 (41.7)	15 (36.6)
Median OS (weeks) (95% CI[a])	30.0 (20.9, 61.1)	38.9 (19.6, 63.3)	25.0 (15.0, NA)	52.4 (25.6, 89.1)	22.4 (15.4, 50.1)

CI = confidence interval; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; NA = not applicable; OS = overall survival.

[a] Median and the 2-sided 95% CI were based on Kaplan-Meier estimate of OS.

Five subjects had a > 30% regression of target tumor lesions. Of these, best overall responses by RECIST 1.1 were PR (3 subjects), SD (1 subject), and PD (1 subject). The 3 subjects with PR were HBV+, the subject with SD was HBV-, and the subject with PD was HBV-.

Percent change in 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) imaging was calculated from screening to the C1D15 assessment as a potential functional imaging biomarker of mTOR pathway inhibition in tumor lesions resulting in altered glucose uptake and metabolism. 19 (35.8%) subjects had ≥ 25% SUV reduction from baseline, 20 (37.7%) had ≥ 15% SUV reduction, and 26 (49.1%) subjects had reduction in uptake that was greater than or equal to 0. The difference between on treatment and baseline values in SUV uptake was statistically significant ($p < 0.0001$).

In addition to these encouraging signals of antitumor activity in HCC, radiologic tumor responses were also observed in all other tumor types but especially in subjects with NSCLC and DLBCL and with rapid symptom improvement in NET carcinoid subjects.

In summary, this study demonstrated preliminary evidence of broad antitumor activity of ATG-008 across multiple solid and hematologic malignancies, with a particularly encouraging signal of activity in subjects with unresectable, sorafenib refractory HCC.

1.3.2.2 CC-223-ST-001 Safety

As of 1 Apr 2014, interim unaudited data are available on 226 subjects treated with ATG-008, including 28 subjects from phase 1 dose escalation, and 198 subjects from phase 2, most of whom started treatment with the MTD of 45 mg QD in continuous cycles of 28 days.

During the dose escalation phase of the study, dose-limiting toxicity (all grade 3) occurred in 4 subjects and included hyperglycemia (30 mg), rash (45 mg), fatigue (60 mg), and mucositis (60 mg). The maximum tolerated dose (MTD) was established to be 45 mg QD.

Preliminary results from this ongoing study as of the SAE database cut-off date of 1 Apr 2014, showed most frequent treatment-emergent SAEs gastrointestinal disorders (18.2%), infections (14.1%), general disorders (8.6%), metabolism and nutritional disorders (7.6%), respiratory disorders (6.6%), renal disorders (5.6%), and others < 5%. The SAEs assessed as being at least possibly related to ATG-008 included blood and lymphatic system disorders (thrombocytopenia), gastrointestinal disorders (abdominal pain, ascites, nausea, vomiting, diarrhea), general disorders (general physical health deterioration, pyrexia), infections and infestations (sepsis, infection, pneumonia), metabolic and nutrition disorders (hyperglycemia, dehydration), renal and urinary disorders (acute renal failure), and respiratory disorders (dyspnoea).

1.3.2.2.1 CC-223-ST-001 Safety in Hepatocellular Carcinoma

During the dose escalation phase (phase 1) of the study, dose-limiting toxicity (all grade 3) occurred in 4 subjects and included hyperglycemia (30 mg), rash (45 mg), fatigue (60 mg), and mucositis (60 mg). The maximum tolerated dose (MTD) was established to be 45 mg QD.

Safety review of the subjects with HCC indication included data from CC-223-ST-001 study (phase 1 and 2). As of the cutoff date of 1 June 2016, 52 (98.1%) out of the 53 subjects enrolled and treated in the HCC cohort in phase 2 experienced at least one treatment-emergent adverse events (TEAE) considered as related to study drug by the Investigator.

The most common related TEAEs were decreased appetite (64.2%), diarrhea (60.4%), fatigue (60.4%), hyperglycemia (60.4%), nausea (50.9%), aspartate aminotransferase increased (43.4%) and pruritus (34%).

As of the CC-223-ST-001 CSR cutoff date of 1 Apr 2014, 28 (52.8%) out of 53 HCC subjects

enrolled in phase 2 reported at least 1 SAE. Eight (15.1%) subjects had at least 1 SAE suspected by the Investigator to be related to ATG-008. The only drug-related SAE reported in more than 1 subject in this cohort was dehydration (in 2 subjects).

Additional SAEs were reported among HCC subjects after the CC-223-ST-001 CSR clinical cutoff date of 01 Apr 2014. As of 01 Jun 2016, 29 (54.7%) subjects reported at least 1 SAE. Eight (15.1%) subjects had at least 1 SAE suspected by the Investigator to be related to ATG-008. The only drug-related SAE reported in more than 1 subject in this cohort was dehydration (in 2 subjects). Which mean no additional SAE relate to ATG-008 were reported after the CSR clinical cutoff date.

Report of the QTcF intervals and the PK-PD relationships for CC-223 and its metabolites revealed that there was no significant effect of CC-223administration on cardiac repolarization or other ECG parameters. Additionally, a review of TEAEs in the CC-223-ST-001 study revealed no clinically significant SAEs, dose reductions or discontinuations due to QTc interval prolongation.

As of the CSR clinical cutoff date, eight deaths out of 53 HCC subjects while on study or during the study-specified follow-up period were reported, including two deaths due to disease progression, two death due to sepsis, and one death due to bacterial sepsis, and one death due to hepatic cancer metastatic, one death due to hepatic encephalopathy, and one death due to hemorrhage intracranial; none was considered related to study drug. No additional deaths occurred in HCC cohort after the CSR clinical cutoff date till 01 Jun 2016.

To date, the overall safety profile appears consistent with published findings for other agents targeting mTOR and related cellular pathways, and is also consistent with preclinical toxicology findings for ATG-008.

1.3.2.3 CC-223-ST-001 Pharmacokinetics

Preliminary PK results in subjects (n = 27) in CC-223-ST-001 phase 1 indicate that ATG-008 is rapidly absorbed with peak ATG-008 plasma levels (T_{max}) achieved between 1 and 3 hours after single and multiple daily doses of ATG-008. Across the dose range of 30 mg to 60 mg, both the maximum observed concentration (C_{max}) and AUC appear to increase in a dose-proportional manner. The terminal half-life of ATG-008 is approximately 4.86 to 5.64 hours. ATG-008 plasma accumulation after multiple dosing was minimal (<25%) after repeated dosing. ATG-008 systemic exposure in humans is not markedly different from that observed in animal species administered multiple oral doses of ATG-008 at or near the maximum tolerated dose in humans (45 mg QD). The major pharmacologically-active metabolite, M1, achieved plasma exposure levels approximately 15-fold greater than parent exposure.

In dose expansion (phase 2) of CC-223-ST-001, ATG-008 and M1 plasma concentrations were measured in all subjects administered 30 or 45 mg QD ATG-008. Following single and multiple oral doses of ATG-008 at dose levels of 30 mg/day and 45 mg/day, ATG-008 was rapidly absorbed with maximum plasma concentrations occurring at a median T_{max} of 1.02 to 2.96 hours. Total body exposures (AUC_{∞}) after a single oral dose of ATG-008 appeared to increase in a dose-proportional manner from 30-mg to 45-mg dose levels. Peak exposures (C_{max}) after a single oral dose also appeared to increase in a dose-proportional manner from 30-mg to 45-mg dose levels. Maximum plasma concentrations of M1 occurred at a median Tmax of 3.08 to 6.13 hours. Total body exposures (AUC_{τ}) of M1 after a single oral dose appeared to increase in a dose-proportional manner from 30mg to 45-mg dose levels. Peak exposures (C_{max}) of M1 after a single oral dose also appeared to increase in a dose-proportional manner from 30-mg to 45-mg dose levels. There was no apparent difference in ATG-008 or M1 PK when comparing across tumor types in phase 2.

Additionally, in HCC subjects following single and multiple oral doses of ATG-008 at dose levels of 30 mg/day and 45 mg/day, ATG-008 was rapidly absorbed with maximum plasma

concentrations occurring at a median T_{max} of 1.0 to 3.0 hours. Total body exposures (AUC_{∞}) after a single oral dose of ATG-008 in subjects with HCC appeared to increase in a dose-proportional manner from 30-mg to 45-mg dose levels. Peak exposures (C_{max}) after a single oral dose of ATG-008 in subjects with HCC also appeared to increase in a dose-proportional manner from 30-mg to 45-mg dose levels. Maximum plasma concentrations of metabolite M1 occurred at a median T_{max} of 5.0 to 14.47 hours. Total body exposures (AUCτ) of M1 in subjects with HCC after a single oral dose appeared to increase in a dose-proportional manner from 30-mg to 45-mg dose levels. Peak exposures (C_{max}) of M1 in subjects with HCC after a single oral dose also appeared to increase in a dose-proportional manner from 30-mg to 45-mg dose levels. There was a significant accumulation of M1 in subjects with HCC upon multiple doses of ATG-008.

Nonclinical in vitro pharmacological assessment of M1 indicates that the metabolite is approximately 1.5 to 2-fold less potent in inhibiting the mTOR pathway compared to ATG-008. In vivo, approximately 5-fold greater exposure of the M1 metabolite is required to achieve similar inhibition of the mTOR pathway compared to ATG-008 in the PC3 human prostate xenograft model. In vitro metabolism studies indicate that M1 is formed via O-demethlyation. Preliminary PK results indicate the terminal half-life of M1 is approximately 2- to 3-fold longer than that of ATG-008. Final PK results are pending study completion.

Pharmacodynamic markers of mTOR kinase inhibition include TORC1 (pS6, p4EBP1) and TORC2 (pAKT) biomarkers in blood using both stimulated and unstimulated assays in monocytes, B cells and T cells. Near maximal inhibition of both TORC1 and TORC2 biomarkers was achieved at peak plasma concentrations achieved in the 30 and 45 mg QD dosing cohorts. PK-pharmacodynamic modeling of inhibition of tumor biomarkers showed near maximal inhibition (approximately 65% to 80%) of both TORC1 and TORC2 markers with drug levels above 100 ng/mL and 200 ng/mL for pS6 and pAKT, respectively. The additive effect of M1, which has a 2- to 3-fold longer half-life than that of ATG-008, may partly explain sustained mTOR inhibition predicted to last 8 to 20 hours. Preclinical EC50 concentrations for these biomarkers were 19 and 69 ng/mL ATG-008, respectively. TORC1 inhibition, assessed using a p4EBP1 assay, also showed concentration dependency, but to a lesser extent than that observed for TORC2 biomarkers. In the expansion phase of the study, TORC1 and TORC2 biomarker inhibition in blood was comparable across all tumor types.

1.3.2.4 Preliminary Clinical Results of Study ATG-008-HCC-001

The preliminary clinical study data up to 24 May 2019 showed that a total of 33 HCC subjects were enrolled (7 subjects received oral ATG008 at the initial daily dose of 15 mg and 26 subjects received 30 mg). Subjects who were treated with ATG-008 were Asian, among which, 13 (39.4%) subjects each from China mainland and Korea, 7 (21.2%) subjects from Taiwan. Of 33 subjects, 16 (48.5%) out of them achieved SD and 13 (39.4%) achieved PD. Another 4 (12.1%) subjects still received the first cycle of treatment and no efficacy evaluation has been performed yet. DCR was 48.5% (16 subjects, 95%CI: 30.8-66.5); approximately half of the subjects (48.5%) had not reported disease progression. The median PFS was 2.0 months (95%CI: 1.9-3.8). The survivors accounted for approximately 78.8% (26/33). The median OS had not achieved (95%CI: 4.8-not achieved). The 3-month survival rate was 96% and 6-month survival rate was 58%. The diameter of the targeted lesions of tumors decreased after treatment from baseline in 42.9% (12/28 subjects) subjects. Among which, the diameter of tumors decreased >20% from baseline in 4 (14.3%) subjects.

All subjects completed the first cycle of study treatment. Subjects who received the longest treatment completed 9 cycles, with the average treatment cycles of 3.2 (±1.6).

The most frequently reported study drug-related TEAEs were skin rash (42.4%), hyperglycemia (36.4%), decreased appetite, stomatitis and pruritus (30.3% each), diarrhea (24.2%), weight loss

(21.2%), fatigue (18.2%), platelet count decreased and white blood cell count decreased (12.1% each), and nausea, AST elevated, neutropenia, blood creatinine increased, proteinuria and hepatic dysfunction (9.1% each).

The most frequently reported Grade 3 and above study drug related TEAEs were hyperglycemia (24.2%), skin rash (18.2%), pruritus (12.1%), stomatitis (9.1%), and fatigue (6.1%).

In summary, preclinical evaluation demonstrates that overall, ATG-008 has an acceptable benefit-to-risk ratio with signals of antitumor activity observed across several tumor types, including encouraging tumor responses in sorafenib-refractory HCC. Data from the first-in-human phase 1/2 study suggest that the safety profile of ATG-008 is comparable in scope to other mTOR pathway inhibitors. Based on the aggregate safety, PK and pharmacodynamic data available, a ATG-008 dose regimen of 30 mg QD has been selected.

According to the previous study results, the sponsor plans to continue to enroll approximately 40 hepatitis B virus (HBV) positive, unresectable HCC subjects who have previously received at least one prior line of systemic therapy. Among which, approximately 20 subjects will receive oral ATG-008 at an initial dose of 45 mg/QD and another 20 subjects will receive oral ATG-008 at an initial dose of 20 mg/BID. The pharmacokinetic (PK) samples will be collected from 10 subjects each in the two dose groups. The monotherapy will be further evaluated in subjects with unresectable, sorafenib-refractory HCC.

The current Investigator's Brochure contains more detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of ATG-008.

1.4 Study Rationale

There remains a high unmet medical need for effective therapies for subjects with unresectable HCC refractory to, or following failure of, at least one prior line of systemic therapy. A strong biologic rationale exists for targeting of the mTOR pathway in HCC, in particular inhibition of pAKT. ATG-008, an mTOR kinase inhibitor targeting both TORC1 and TORC2 complexes, has demonstrated promising preclinical and clinical activity against HCC, especially in HBV+ HCC subjects. Furthermore, resistance to sorafenib can be mediated by mTOR pathway activation lending further support to the development of ATG-008 in unresectable HCC in the second-line setting.

As described earlier, the greatest incidence and mortality of HBV+ HCC patients are in Asian countries (especially in China), and this contrasts sharply with western countries. It is critical to have effective treatment for patients failed at least one prior line of systemic therapy in Asian subjects.

- **Clinical efficacy: compared to the study results of Celgene, the current preliminary clinical study data of this study showed that ATG-008 treatments with 15 mg and 30 mg were effective, but the expected tumor control rate had not been observed yet. It was preliminarily considered that the best dose range of ATG-008 might have not been achieved.**

According to the results of study CC-223-ST-001-B which has been completed by Celgene, the ORR of solid tumor HCC cohort was 5.7% (3/53), among which, the best efficacy of 3 subjects (all had positive HBV) was PR and 2 of them were treated with 45 mg/QD ATG-008 (the maximum tolerated dose [MTD] of ATG-008 monotherapy was 45 mg/day, the intolerable dose was 60 mg/day).

As of 18 Jul 2019, the preliminary clinical study data showed that this study enrolled a total of 35 HCC subjects (all were Asian, among which, 15 subjects were from Chinese mainland, 13 from

Korea and 7 from Taiwan. 7 subjects received oral ATG-008 at the initial daily dose of 15mg and 28 subjects received 30mg). Among 35 subjects, 1 subject achieved PR, 14 subjects achieved SD, 19 subjects achieved PD and 1 subject still received the first cycle of treatment and no efficacy evaluation has been performed yet. The survivors accounts for approximately 65.7% (23/35). The diameter of the targeted lesions of tumors decreased after treatment from baseline in 38.2% (13/34) subjects. Currently, subjects who received the longest treatment had completed 11 cycles of treatment.

- **Clinical safety: the safety profile currently observed in this study was similar to the results of foreign studies completed by Celgene and that of mTOR targeted drugs**

The most common related TEAEs in study CC-223-ST-001 completed by Celgene were decreased appetite (64.2%), diarrhea (60.4%), fatigue (60.4%), hyperglycemia (60.4%), nausea (50.9%), aspartate aminotransferase increased (43.4%) and pruritus (34%).

No suspected and unexpected serious adverse reactions (SUSAR) were reported in this study. One case of DLT was observed in 15mg dose group and no DLT in 30mg group. The most frequently reported study drug-related TEAEs were skin rash and hyperglycemia (45.7% each), decreased appetite and pruritus (31.4% each), diarrhea and stomatitis (28.6% each), weight loss (22.9%), fatigue and platelet count decreased (20.0% each), white blood cell count decreased, mouth ulceration and proteinuria (17.1% each), nausea, hepatic dysfunction and hand-foot syndrome (14.3% each), discomfort and AST elevated (11.4% each).

As ATG-008 is firstly and orally administered hepatitis B virus (HBV) positive, HCC Asian subjects who have previously received at least one prior line of systemic therapy in this study, the overall safety profile of ATG-008 is similar to that of foreign clinical studies in Europe and America, and no unexpected new safety signal is reported, it is further confirmed that ATG-008 is well tolerated and further dose escalation is allowed.

- **Clinical PK: the PK profile of this study was similar to the PK profile of foreign patients in Europe and America**

The foreign study (Europe and America) CC-223-ST-001-Part A demonstrated that the unchanged ATG-008 showed linear relationship within the dose range of 7.5 mg~60 mg, and the exposure level of metabolite M1 also presented linear relationship with the dose.

The preliminary PK results of this study (ATG-008 15 mg and 30 mg) showed that the exposure level of active compound and its metabolite presented linear relationship with the dose. Compared with PK parameters of foreign studies in Europe and America, the active compound had numerically higher C_{max} and shorter T_{max}. The active compound and its metabolite had similar elimination rate (in different dose groups). Analysis of difference in PK parameters in Europe, America and Asia showed that the difference in exposure level mainly caused by C_{max} difference, which might be related to lighter body weight and smaller volume of distribution of Asian patients.

According to the currently available data, it was estimated that the exposure level of 20 mg/BID might be lower than that of 45 mg/QD, supporting that the administration mode BID could be explored in this study.

According to the above clinical efficacy, safety and PK study results, the sponsor proposes to add 2 dose groups, i.e., 45 mg/QD and 20 mg/BID (approximately 20 subjects each), to further explore and evaluate the PK, safety, tolerability and efficacy of ATG-008 in advanced HBV+ HCC subjects.

1.4.1 Rationale for Dose of ATG-008

In CC-223-ST-001, frequent dose reductions, especially in 45-mg dose HCC subgroup, were

required due to mitigate toxicity: The numbers of subjects with dose reductions for subjects starting at the 30 mg and 45 mg dose levels were 12/28 (42.9%) and 18/25 (72.0%), respectively; median time to first dose reduction due to a TEAE was 43.0 days and 26.5 days, respectively.

Despite the dose reductions, encouraging signals of activity were observed in the HCC cohort including three subjects that met the criteria for radiologic PR (> 30% reduction in target lesions) at the first restaging evaluation after 2 cycles of treatment, reduction in SUV uptake by PET, and reductions in AFP. All 3 HCC subjects in phase 2 with radiologic PR were HBV+, required dose reduction to 30 mg.

Based on the high frequency of dose reductions, 45 mg daily was not considered to be an acceptable dose for further study in unresectable HCC. A dose of 30 mg daily was well tolerated in most subjects and resulted in near maximal mTOR biomarker [pAKT, pS6 and phosphorylated 4E-binding protein 1 (P4EBP1)] inhibition in blood with at least 40% to 70% inhibition of each marker. Plasma ATG-008 drug exposures at 30 mg also exceeded levels associated with mTOR biomarker inhibition and antitumor activity in preclinical tumor xenograft models. In addition, the most durable tumor response was observed in a subject with breast cancer at the 30-mg dose level during phase 1 of the study. Antengene believes these data support the selection of 30 mg QD as the most appropriate dose of ATG-008 and 15 mg QD and 30 mg QD for PK study in unresectable HCC in the study.

Moreover, the pre-clinical study results (Study AP2908) showed that ATG-008 treatment group had dose- and dosing regimen- dependent tumor inhibition: when the drug was administered at 5 and 10 mg/kg BID, it was demonstrated that significant dose-dependent tumor volume decrease was observed under the two dose levels (65% and 80% in 5 and 10 mg/kg, respectively, $p<0.001$). After the last administration, the total plasma AUC_{10h} was 8.6 and 23.7 μM·h in 5 and 10mg/kg dose levels, respectively. The 65% tumor volume decrease confirmed that the minimum effective dose required to inhibit PC3 tumor growth was 5 mg/kg BID. In PC3 tumors, the PK/PD relationship indicated that > 80% inhibition of pS6RP and > 60% inhibition of pAKT Ser473 were obtained at total drug plasma concentrations greater than 0.2 μM. Maintenance of plasma levels > 0.2 μM and this degree of biomarker inhibition degree through BID dosing for 8 hours confers good anti-tumor efficacy in PC3 tumors. U87MG human glioblastoma and xenograft models of HCT-116 human colorectal tumor also showed that ATG-008 had dose and dosing regimen-dependent tumor inhibition. Moreover, approximately 50% of HCT-116 tumor volume decrease was observed at the dose level of 10 mg/kg BID.

According to the results of study CC-223-ST-001-B which has been completed by Celgene, substantial biomarker inhibition of p4E-BP1 (>40% median inhibition at C1D15-1.5 hours) and pAKT (>70% median inhibition at C1D15-1.5 hours) had been achieved under MTD of the dose of 45 mg/QD. The median inhibition rate of p4E-BP1 and pAKT after the first dosing was slightly lower at the lower dose of 30 mg/QD. However, during the later administration period, inhibition of two biomarkers had no dose-related difference.

In addition, according to the results of study CC-223-ST-001-B which has been completed by Celgene, the ORR of solid tumor HCC cohort was 5.7% (3/53), among which, the best efficacy of 3 subjects (all had positive HBV) was PR and 2 of them were treated with 45 mg/QD ATG-008 (the maximum tolerated dose (MTD) of ATG-008 monotherapy was 45 mg/day, the intolerable dose was 60 mg/day). Compared to the study results of Celgene, the current preliminary clinical study data of this study showed that ATG-008 treatments with 15 mg and 30 mg were effective, but the expected tumor control rate had not been observed yet. It was preliminarily considered that the best dose range of ATG-008 might have not been achieved.

Meanwhile, the PK profile of this study was similar to the PK profile of foreign patients

(indicating that PK profile of ATG-008 showed linear relationship). Based on the clinical observation results, low dose of ATG-008 can achieve steady state plasma concentration at which the drug exert effect, indicating that the administration mode of BID at a low dose may have certain advantage on maintaining effective steady state concentration compared to the administration mode of QD.

According to the above bases, this study proposes to add 2 dose groups, i.e., 45 mg/QD and 20 mg/BID (approximately 20 subjects each), to further explore and evaluate the PK, safety, tolerability and efficacy of ATG-008 in advanced HBV+ HCC subjects.

2. STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate pharmacokinetics (PK), safety, tolerability and overall response rate (ORR) of ATG-008 in HBV+ HCC subjects who have received at least one prior line of systemic therapy.

2.2 Secondary Objectives

- To evaluate overall survival (OS)
- To evaluate time to progression (TTP)
- To evaluate progression-free survival (PFS)
- To evaluate disease control rate (DCR)
- To evaluate duration of response (DOR)
- To evaluate time to response (TTR)
- To evaluate survival rate

3. STUDY ENDPOINTS

3.1 Primary Endpoint

- C_{max}, AUC, t_{max}, $T_{1/2}$, CL/F and Vd/F of ATG-008 and M1 after single and multiple doses.
- The incidence of treatment emergent adverse events (TEAEs), SAEs, laboratory abnormalities and other safety parameters
- ORR: Percentage of subjects with PR, or CR

3.2 Secondary Endpoints

- Kaplan-Meier estimate of OS
- TTP: the time from the first dose date until disease progression
- PFS: the time from the first dose date until disease progression or death from any cause
- DCR: the percentage of subjects with CR, or PR or stable disease (SD)
- DOR: the time from the criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented
- TTR: the time from the first dose date to the first documentation of response of PR or better.
- 6, 9 and 12 month of survival rate (percentage of patients alive)

4. OVERALL STUDY DESIGN

4.1 Study Design

ATG-008-HCC-001 is a MRCT trial in which ATG-008 will be administered orally in HBV+ HCC subjects who have received at least one prior line of systemic therapy in Asian countries. The trial is designed as an open-label phase 2 trial to assess PK, safety, tolerability and efficacy of oral ATG-008 administered until the appearance of radiologic disease progression (according to RECIST 1.1). The PK and safety profiles will be compared with historical ATG-008 results when

data are available.

According to the previous study results, the sponsor will plan to continue to enroll approximately 40 hepatitis B virus (HBV) positive, unresectable HCC subjects who have previously received at least one prior line of systemic therapy. Among which, approximately 20 subjects will receive oral ATG-008 at an initial dose of 45 mg/QD and another 20 subjects will receive oral ATG-008 at an initial dose of 20mg/BID. The pharmacokinetic (PK) samples will be collected from 10 subjects each in the two dose groups so as to further evaluate the PK profile of ATG-008 and its metabolites.

If the overall response rate (ORR) of tumor is greater than 15% in the study dose group (45 mg/QD or 20 mg/BID), then this study will be expanded to enroll additional approximately 110 subjects using ORR as the primary study endpoint, to further evaluate the efficacy and safety of ATG-008.

At the discretion of the Investigator, treatment may continue beyond radiologic progression until symptomatic deterioration if no other therapeutic options are available. Subjects may also receive best supportive care according to local practice. All subjects will continue to be followed after treatment discontinuation for radiologic tumor response until disease progression, death or withdrawal of consent (as defined in Section 6.4, if applicable) and new anticancer treatments until death or withdrawal of consent. Subjects will also be followed for survival until death or withdrawal of consent.

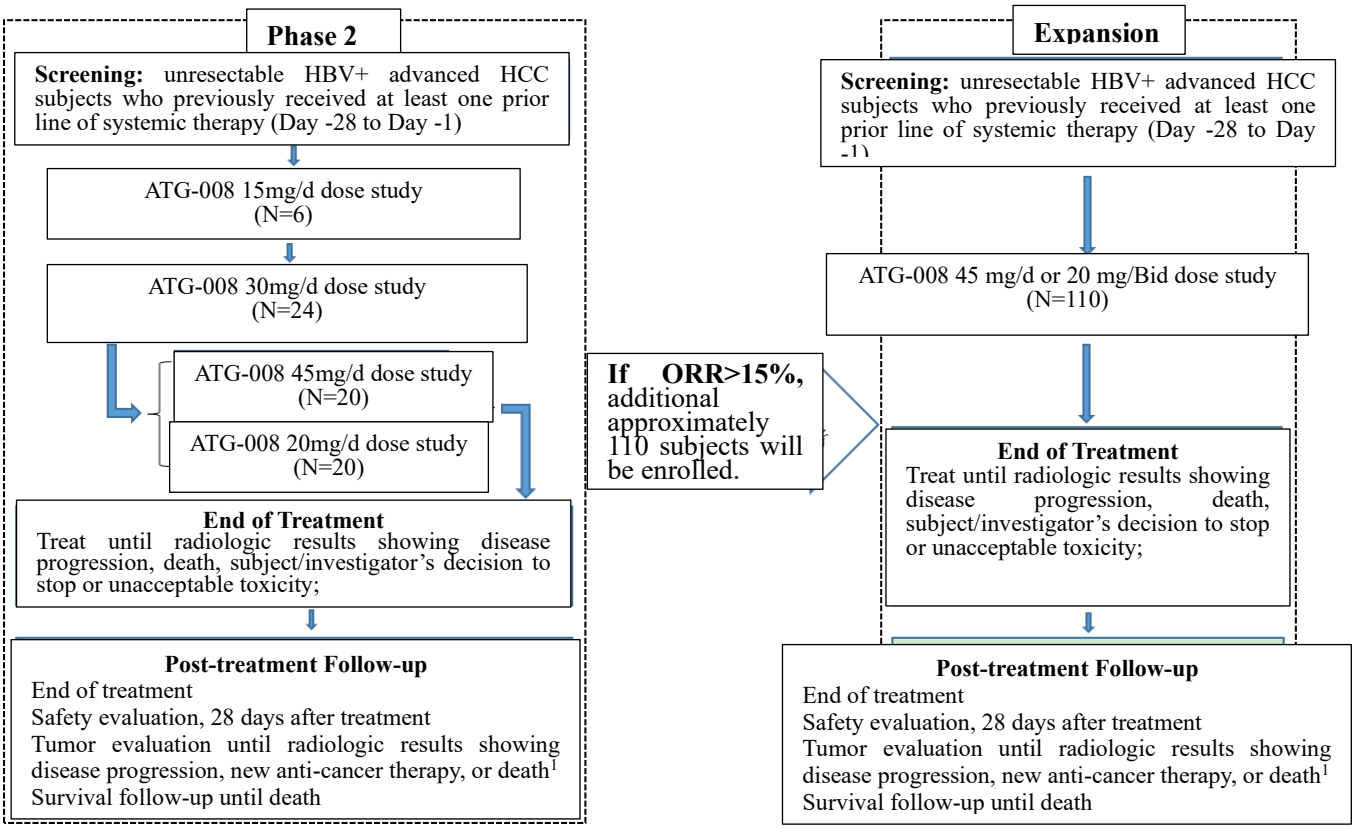
The starting dose of ATG-008 will be 15 mg daily for 28 days each cycle for the first 6 fully evaluable (including PK outcomes) subjects. Providing DLTs occur in less than 2 of 6 subjects who complete Cycle 1, additional 24 subjects will be enrolled at the starting dose of 30 mg daily. Subjects who tolerated the 15-mg dose level for at least 1 cycle may then dose-escalate to 30 mg at the Investigator's discretion.

DLTs included hyperglycemia, rash, fatigue, and mucositis, any of which ≥ grade 3, based on CC-223-ST-001 results.

The trial will consist of the following periods:

- ☐ Screening (see Section 6.1)
- ☐ Treatment (see Section 6.2)
- ☐ End of treatment (see Section 6.2.1)
- ☐ Follow-up (see Section 6.3)

Figure 1: Overall Study Design



Abbreviations: HCC = hepatocellular carcinoma
[1] Evaluations also may stop if the subject withdraws consent, or is lost to follow-up.

4.2 Study Design Rationale

The HCC subject population who received at least one prior line of systemic therapy represents a setting of high unmet need for which few effective therapies are currently available. Strong biologic rationale exists for targeting both the TORC1 and TORC2 signaling pathways in this disease. High basal mTOR pathway activation, including pAKT, is mediated through multiple genetic and epigenetic mechanisms and is present in the majority of HCC tumors. Furthermore, PI3K/mTOR pathway activation represents a potential mechanism of resistance to sorafenib. Encouraging signals of anti-tumor activity with ATG-008, including radiologic tumor regression and prolonged SD, have been observed and warrant further investigation of this drug in this population.

The selected ATG-008 dose of 30 mg QD represents a dose with an acceptable safety and activity profile and anticipated dose reductions in less than 30% of subjects. While 45 mg QD was established as the MTD during the phase 1 dose escalation of the CC-223-ST-001 study, further experience with this dose during the expansion phase demonstrated an unacceptably high rate of dose reductions due to toxicity. Following dose reduction to 30 mg QD, most subjects were able to tolerate this lower dose without further dose modifications. Drug exposures at 30 and 45 mg demonstrated near maximal mTOR pathway inhibition in blood of both TORC1 (by pS6) and TORC2 (by pAKT) at both dose levels. Clinical antitumor activity was observed at 30 mg QD including a durable PR in a subject with breast cancer treated in the 30-mg dose escalation cohort.

An open-label trial is acceptable and appropriate given limited effective second-line and later

therapies in unresectable HCC. The high frequency of HCC in the Asia-Pacific region warrants inclusion of Asian countries in this MRCT study.

The starting dose of ATG-008 will be 15 mg daily for 28 days each cycle for the first 6 fully evaluable (including PK outcomes) subjects. Providing DLTs occur in less than 2 of 6 subjects who complete Cycle 1, additional 24 subjects will be enrolled at the starting dose of 30 mg daily. Subjects who tolerated the 15-mg dose level, may then dose-escalate to 30 mg at the Investigator's discretion until enrollment of 30-mg group starts.

As of 18 Jul 2019, the preliminary clinical study data showed that this study enrolled a total of 35 HCC subjects (all were Asian, among which, 15 subjects were from Chinese mainland, 13 from Korea and 7 from Taiwan). 7 subjects received oral ATG-008 at the initial daily dose of 15 mg and 28 subjects received 30 mg). Among 35 subjects, 1 subject achieved PR, 14 subjects achieved SD, 19 subjects achieved PD and 1 subject still received the first cycle of treatment and no efficacy evaluation has been performed yet. The survivors accounts for approximately 65.7% (23/35). The diameter of the targeted lesions of tumors decreased after treatment from baseline in 38.2% (13/34) subjects. Currently, subjects who received the longest treatment had completed 11 cycles of treatment.

No suspected and unexpected serious adverse reactions (SUSAR) were reported in this study. One case of DLT was observed in 15 mg dose group and no DLT in 30 mg group. The most frequently reported study drug-related TEAEs were skin rash and hyperglycemia (45.7% each), decreased appetite and pruritus (31.4% each), diarrhea and stomatitis (28.6% each), weight loss (22.9%), fatigue and platelet count decreased (20.0% each), white blood cell count decreased, mouth ulceration and proteinuria (17.1% each), nausea, hepatic dysfunction and hand-foot syndrome (14.3% each), discomfort, and AST elevated (11.4% each).

Consequently, ATG-008 is firstly and orally administered hepatitis B virus (HBV) positive, HCC Asian subjects who have previously received at least one prior line of systemic therapy in this study, the preliminary efficacy has been observed, the overall safety profile of ATG-008 is similar to that of previous foreign clinical studies and similar drugs, and no unexpected new safety signal is reported, it is further confirmed that ATG 008 is well tolerated.

In addition, according to the results of study CC-223-ST-001-B which has been completed by Celgene, the ORR of solid tumor HCC cohort was 5.7%, among which, the best efficacy of 3 subjects (all had positive HBV) was PR and 2 of them were treated with 45 mg ATG-008 daily (the maximum tolerated dose (MTD) of ATG-008 monotherapy was 45 mg/day, the intolerable dose was 60 mg/day).

Considering the observed preliminary efficacy and favorable safety and tolerability of ATG-008, this study proposes to continue to enroll approximately 40 subjects to receive ATG-008 at an initial dose of 45 mg/QD or 20 mg/BID (approximately 20 subjects each) to further evaluate the PK, safety, tolerability and efficacy of ATG-008.

If ORR of tumor is greater than 15% in the study dose group (45 mg/QD or 20 mg/BID), then this study will be expanded to enroll additional approximately 110 subjects using ORR as the primary study endpoint, to further evaluate the efficacy and safety of ATG-008.

4.3 Study Duration

The screening period will last up to 28 days. Once treatment begins, subjects will remain on ATG-008 until radiologic disease progression (according to RECIST 1.1), toxicity, subject or physician decision, withdrawal of consent, or death. It is expected that most subjects will receive study drug for 1 to 12 months. If treatment is discontinued for reasons other than disease

progression or death or withdrawal of consent, subjects will be followed for radiologic progression until disease progression. Regardless of treatment status, all subjects will be followed for survival until death or study discontinuation.

According to the previous study results, the sponsor will continue to enroll approximately 40 subjects. Approximately 6 months are needed for enrollment period. Completing PK (PK samples will be collected from 10 subjects each in the two dose groups), safety and preliminary efficacy evaluations is expected to take approximately 6 months.

4.4 End of Trial

The end of Study is defined as either the date of the last visit of the last subject to complete the trial, or the date of receipt of the last data point (e.g., date of death) from the last subject that is required for analysis, whichever is the earlier date.

5. TABLE OF EVENTS

Table 3: Table of Events

	Screening Period	Treatment Period								Follow-up Period
	Screening	Cycle 1 (single dosing)		Cycle 1 (continuing dosing)		Cycle 2		Subsequent cycles	End of Treatment	
Study Day[a]	**-29 to -2[b]**	**-1**	**0**	**1**	**15**	**1**	**15**	**1**		**Disease progression/ survival**
Study Entry										
Informed consent	X									
Prior cancer history	X									
Prior cancer therapies[c]	X									
Demographics	X									
Complete medical history	X									
Prior/ concomitant medication evaluation	X			Continuous, until 28 days after treatment discontinuation						
Prior/ concomitant procedures evaluation	X			Continuous, until 28 days after treatment discontinuation						
Inclusion/exclusion criteria	X									

Table 3: Table of events (continued)

	Screening Period	Treatment Period								Follow-up Period
	Screening	Cycle 1 (single dosing)		Cycle 1 (continuing dosing)		Cycle 2		Subsequent cycles	End of Treatment	
Study Day[a]	**-29 to -2[b]**	**-1**	**0**	**1**	**15**	**1**	**15**	**1**		**Disease progression/ survival**
Investigational Product										
Administer ATG-008		X		Daily, continuously						
Safety Assessment										
Adverse event collection	Continuous starting after informed consent signature, until 28 days after last dose of IP									
Weight	X			X		X		X	X	
Height	X									
Vital signs	X			X	X	X	X	X	X	
Hematology laboratory	X(-7 to -1)				X	X	X	X	X	
Coagulation function test	X(-7 to -1)					X		X		
Fasting chemistry laboratory test	X(-7 to -1)				X	X	X	X	X	
Special chemistry: Amylase, lipase, TSH, fT4	X(-7 to -1)					X		X		

Table 3: Table of events (continued)

	Screening Period	Treatment Period								Follow-up Period
	Screening	Cycle 1 (single dosing)		Cycle 1 (continuing dosing)		Cycle 2		Subsequent cycles	End of Treatment	
Study Day[a]	**-29 to -2[b]**	**-1**	**0**	**1**	**15**	**1**	**15**	**1**		**Disease progression/ survival**
HbA1c	X(-7 to -1)							Every other cycle starting in Cycle 3		
AFP	X					X		X	X	
HBV and HCV serologies (HBsAg, HBeAg, HBsAb, HBeAb, HBcAb, HCVAb)	X									
HBV viral load[d]	X					X		X		
Urine routine	X(-7 to -1)				X	X	X	X		
12-lead electrocardiogram (local assessment)	X								X	
Serum β-hCG (in FCBP)	X			As clinically indicated						
Urine β-hCG（FCBP）	X[e] (-72 hrs to 0 hr from dosing)					X		X	X	
PK samples(blood)[f]		X	X	X	X					
PK samples (urine)[g]		X	X							

Table 3: Table of events (continued)

	Screening Period	Treatment Period								Follow-up Period
	Screening	Cycle 1 (single dosing)		Cycle 1 (continuing dosing)		Cycle 2		Subsequent cycles	End of Treatment	
Study Day[a]	**-29 to -2[b]**	**-1**	**0**	**1**	**15**	**1**	**15**	**1**		**Disease progression/ survival**
Efficacy Assessments										
Tumor assessments (CT/MRI, see Section 6.4)	X			Every 8 weeks (± 5 days) from enrollment (first dose), until radiologic progression						
ECOG performance status	X			X		X		X	X	
Follow-up										
Survival follow-up										Every 8 weeks (± 1 week)
Anticancer therapy after treatment discontinuation										Every 8 weeks (± 1 week)

[a] All visits have a ± 3 day window, except Cycle 1 Day 1 (which must occur within 28 days of signing the ICF).
[b] Screening assessments must be performed prior to study treatment, however these events may occur on the same calendar day as long as the chronological order is followed.
[c] Prior cancer therapies includes surgery, radiation, systemic, locoregional or any other therapy (e.g. hormonal) for the subject's cancer.
[d] HBV viral load is collected in subsequent cycles only in subjects with chronic HBV infection, positive HBeAg, positive HBcAb or positive viral load at screening.
[e] Urine β-hCG (or local serum) at screening within 72 hours of Cycle 1 Day -1 dose.
[f] PK samples (blood) should be taken at each scheduled day, according to the schedule in Section 6.5.1.
[g] PK samples (urine) should be taken at each scheduled day, according to the schedule in Section 6.5.2.

6. PROCEDURES

6.1. Screening Period

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 28 days of first dosing except as noted below (e.g., eligibility laboratory assessments). All screening assessments must be performed prior to enrollment (first dose) and subsequently treatment, however these events may occur on the same calendar day as long as the chronological order is followed.

Any questions regarding subject eligibility should be directed to the Antengene Medical Monitor or designee. Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

Unless otherwise specified, all laboratory analysis will be performed at site. Screening eligibility criteria laboratory values must be performed within 7 days of the first dose of study drug and demonstrate subject eligibility. Screening assessments may be repeated within the screening window if necessary, and the most recently obtained result should be used to demonstrate eligibility. Other laboratory evaluations not specifically designated to be performed within 7 days of the first dose of study drug can be performed at any time during Screening, however for convenience it is recommended they be collected at the same time. The screening assessments which are study specific (such as assessment samples need to be taken and sent centrally) and are belong to local clinical routine practice, can be accepted if they are done before ICF taken.

Subjects should fast for at least 6 hours prior to those clinical visits which require evaluation of PK and fasting chemistry examination.

The following will be performed at screening and specified in the Table of Events, Table 3:

- Informed consent.
- Demographics (age, gender, race, height, weight, region).
- Prior cancer history (including specific information regarding diagnosis, staging, and histology).
- Prior cancer therapies: Includes surgery, radiation, systemic, locoregional, or any other therapy (e.g. hormonal) for the subject's cancer (reason for discontinuation of prior therapies, e.g. disease progression, intolerance or others, should be recorded as well).
- Medical history (includes relevant medical conditions occurring > 28 days before screening should also be included).
- Prior and concomitant medication evaluation (includes those taken ≤ 28 days before the screening visit, except those taken for cancer which are recorded as part of prior cancer therapy).
- Prior and concomitant procedures (includes all procedures occurring ≤ 28 days before the screening visit).
- Adverse event evaluation (begins when the subject signs the informed consent form [ICF]).
- Vital signs (including blood pressure, temperature and pulse).
- Hematology: Complete blood count (CBC) with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count with absolute differentials (neutrophils, lymphocytes, monocytes, eosinophils and

basophils), and platelet count; within 7 days of the first dose of study drug.

- Coagulation panel: Prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT); within 7 days of the first dose of study drug.
- Fasting chemistry laboratory: Includes sodium, potassium, chloride, calcium, magnesium, phosphorus, glucose, blood urea nitrogen (BUN), creatinine, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), aspartate amino transferase (AST/SGOT), alanine amino transferase (ALT/SGPT), lactate dehydrogenase (LDH), uric acid, cholesterol and triglycerides; within 7 days of the first dose of study drug.
- Special chemistry laboratory: Amylase, lipase, thyroid stimulating hormone (TSH), free T4 (fT4); within 7 days of the first dose of study drug.
- Hemoglobin A1c (HbA1c) within 7 days of the first dose of study drug.
- AFP.
- Hepatitis B virus (HBV) and hepatitis C virus (HCV) serologies (hepatitis B surface antigen [HBsAg], hepatitis B e antigen [HBeAg], hepatitis B surface antibody [HBsAb], hepatitis B e antibody [HBeAb], hepatitis B core antibody [HBcAb], hepatitis C virus antibody [HCVAb]).
- HBV viral load.
- Urine routine within 7 days of the first dose of study drug.
- 12-lead electrocardiogram (ECG), single local assessment; when an ECG time-point coincides with any other assessment, the ECG should always be collected first.
- Pregnancy test (β-hCG) is required for all female subjects of child-bearing potential. Serum β-hCG pregnancy test will be performed at screening. A urine (or local serum) pregnancy test will be performed to assess subject eligibility within 72 hours prior to the first administration of study drug.
- Response assessment/tumor evaluation (see Section 6.4). Tumor scans (CT/MRI) evaluable per RECIST 1.1 performed ≤ 28 days prior to first dose of study drug need not be repeated for the purposes of screening. For stratification purposes, macroscopic vascular invasion is defined as HCC involvement of branches of portal or hepatic veins detected by gross pathological examination or radiological imaging; extrahepatic spread is defined as HCC involvement of organs or lymph nodes outside liver.
- ECOG performance status.

6.2. Treatment Period

After signed the ICF within 28 days, the eligible subjects must start treatment as soon as possible. For all subsequent visits, an administrative window of ± 3 days is permitted, otherwise specified.

Subjects will receive a single dose of ATG-008 on Day -1, followed by a 48-hour observation for PK sample collection.

- Oral daily dosing of 15 mg or 30 mg begin on Day 1 and will continue in 28-day cycles
- It is planned that approximately 20 subjects will receive oral ATG-008 at an initial dose of 45 mg/QD and another 20 subjects will receive oral ATG-008 at an initial dose of 20 mg/BID. The 28 continuous days are regarded as one treatment cycle. The pharmacokinetic (PK) samples will be collected from 10 subjects each in the two dose groups.

The subjects will continue to use ATG-008 until radiologic disease progression, intolerable toxicities, or withdrawal of consent for further dosing (in which case subjects will continue to be followed for further anticancer treatment and survival status unless consent for this has been explicitly withdrawn). Subjects will fast ⩾ 6 hours before those clinical visits which require evaluation of PK and fasting chemistry examination. PK, safety and tolerability for the 30-mg dose level will follow the assessment of the 15-mg dose level if DLTs occur in less than 2 of 6 subjects at the 15-mg dose level who complete Cycle 1.

The following evaluations will be performed at the frequency specified in the Table of Events, Table 3. The evaluations should be performed prior to dosing on the visit day, unless otherwise specified.

- Adverse event evaluation (continuously)
- Concomitant medications evaluation (including medications for best supportive care)
- Concomitant procedures evaluation
- ECOG performance status
- Vital signs, weight
- Hematology laboratory
- Coagulation panel
- Fasting chemistry laboratory
- Special chemistry laboratory
- HbA1c
- Urine routine
- AFP
- HBV viral load (in subjects with positive HBsAg, HBeAg HBcAb or positive viral load at screening).
- Urine β-hCG (females of childbearing potential (FCBP) only)
- Radiologic response assessment/tumor evaluation and assessment of disease progression (see Section 6.4)

- PK sampling (see Section 6.5)

Detailed evaluations are listed in Table 3.

6.2.1 End of Treatment

An end of treatment (EOT) evaluation should be performed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made.

The following evaluations will be performed as specified in the Table of Events:

- Adverse event evaluation
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Vital signs and weight.
- Hematology laboratory
- Fasting chemistry laboratory
- AFP
- 12-lead ECG, single local assessment
- Urine β-hCG (FCBP only)

For subjects who discontinue study drug for reasons other than radiologic progression (or withdrawal of consent for additional follow-up procedures), tumor evaluations will be continued at the schedule defined in the Table of Events Table 3, and do not need to be performed specifically for the EOT visit.

6.3. Follow-up Period

6.3.1 28-day Follow-up

All subjects will be monitored for reporting of new or follow-up of existing AEs for 28 days after the last dose of study drug. Any clinically relevant assessments or laboratory parameters should have unscheduled assessments conducted until resolution, at the discretion of the Investigator.

6.3.2 Efficacy Follow-up

All subjects who discontinue treatment for reasons other than disease progression, death or withdrawal of consent for post-treatment follow-up procedures will continue to undergo response assessments and collection of new anticancer therapies as specified in Section 6.4.

6.3.3 Survival Follow-up

After the last dose of study drug, all subjects will be followed every 8 weeks (± 1 week) for survival until death or lost to follow-up. Even when subjects withdraw consent for further treatment, every effort should be made to obtain post-treatment follow-up information which includes new anticancer therapies and survival status.

Survival follow-up may be conducted by record review and/or telephone contact with the subject, family or the subject's treating physician.

6.4. Response Assessments

Tumor response assessments should be performed in Screening (up to 28 days before the start of study drug) and every 8 weeks (± 5 days) from the first dose date until disease progression, death or withdrawal of consent from additional follow-up procedures. Tumor

assessments includes imaging (CT or MRI) of the chest, abdomen and pelvis at baseline. Subjects with brain lesions will have brain scans at screening and at each tumor assessment. After Screening, tumor assessments will be performed on completion of C2, C4 and C6 (i.e,, C3, 5 and 7/Day1±7 days) using the same scanning modalities used at baseline. Corticosteroids (if used) dosage must be stable ≥ 5 days prior to all scans. EOT scan need not be repeated if prior scan was < 28 days.

If a subject discontinues study drug due to toxicity, subject or physician decision, the collection of response assessments should continue at the same schedule. Additionally, if a subject continues treatment beyond radiologic disease progression until symptomatic deterioration (see Appendix A, Section 19.1.2.4), tumor evaluations should continue until study drug is stopped. Evaluation of response should be performed using RECIST 1.1 guidelines.

New anticancer therapy includes any systemic medication, locoregional therapy, surgery, radiation or any other therapy intended to treat the subject's cancer.

6.4.1 Assessment of Radiologic Response According to RECIST 1.1

Response will be assessed using RECIST 1.1 Appendix. Response assessments (tumor evaluations) include computed tomography (CT) scan or magnetic resonance imaging (MRI). The regions to be imaged are the chest, abdomen and pelvis, as well as any other region clinically indicated for tumor imaging. Subjects with brain metastases will have brain scans at Screening and at each tumor reassessment. The same mode of imaging for lesion evaluation at screening must be consistently used throughout the study.

The CT imaging should include contrast unless medically contraindicated. Conventional CT should be performed with contiguous cuts of 5 mm or less in slice thickness. Spiral CT should be performed by use of a 5 mm contiguous reconstruction algorithm.

All subjects with evidence of radiologic tumor response (CR or PR) should have the response confirmed with repeat assessments at the next scheduled scan, but after no less than 28 days. Response assessments must have occurred ≥ 5 weeks from the first dose date to be considered as SD for a best response.

The Investigators will evaluate RECIST 1.1 response after each restaging and overall assessment. All related scans will be collected and saved for future independent central review.

If ORR of tumor is greater than 15% in the study dose group (45 mg/QD or 20 mg/BID), then this study will be expanded to enroll additional approximately 110 subjects using ORR as the primary study endpoint, to further evaluate the efficacy and safety of ATG-008.

All scans will be collected and then be reviewed centrally for independent analysis of ORR and other objective tumor response outcomes. mRECIST will then also be applied in tumor assessment, if necessary.

Additional details and definitions of response according to RECIST 1.1 are found in Appendix A in Section 19.1.

6.5. Pharmacokinetics

PK blood samples (2 mL/sample) will be collected from each subject as described in Table 3.

For all PK draws, the following information will be documented: The dose of study drug administered, the actual time of study drug dosing, the actual time of each PK sample collection, and the nominal or scheduled time for PK sample collection. The laboratory manual includes procedures for collecting, processing, storing, and shipping PK samples.

6.5.1 Intense Blood Sampling

A total of 30 subjects will undergo intense PK sampling; 6 subjects at the 15-mg dose and 24 subjects at the 30-mg dose level.

As for the 2 dose groups 45 mg/QD and 20 mg/BID, PK samples of 10 subjects each should be collected.

Blood (2 mL/sample) will be drawn at the following times in Cycle 1.

Sampling time points for subjects received ATG-008 at the initial doses of 15 mg, 30 mg and 45 mg/QD:

On Day -1: 0hr (< 15min prior to dosing), 0.5hr ± 5 mins, 1hr ± 10mins, 1.5hr ± 10mins, 3hr ± 10mins, 5hr ± 15mins, 8hr ± 30mins, 24hr ± 60mins and 48hr ± 60mins after the first dose of ATG-008
On Day 15: 0hr (< 15min prior to dosing), 0.5hr ± 5mins, 1hr ± 10mins, 1.5hr ± 10mins, 3hr ± 10mins, 5hr ± 15mins, 8hr ± 30mins and 24hr ± 60mins after the Day 15 dose.

Sampling time points for subjects received ATG-008 at the initial dose of 20 mg/BID:

At Day -1: 0hr (15 minutes before dosing); the first dose of 20 mg: 0.5hr ±5min, 1hr±10min, 1.5hr±10min, 3hr±10min, 5hr±15min, 8hr±30min and 12hr±30min; second dosing of 20 mg: 12hr±30min after dose of ATG-008;

At Day 15: 0hr (15 minutes before dosing); the first dose of 20 mg: 0.5hr ±5min, 1hr±10min, 1.5hr±10min, 3hr±10min, 5hr±15min, 8hr±30min and 12hr±30min after dose of ATG-008;

When study drug dosing has been interrupted before the Day 15 assessments, PK sampling should be delayed until ATG-008 has been administered continuously for at least 7 days in order to more accurately determine steady state kinetics.

After Day 15, if the dose of ATG-008 is reduced and (optional) subject consent is obtained, approximately 10 days later blood will be withdrawn for additional PK assessments at the following times in order to conduct intrasubject assessment of PK at lower dose levels: Predose (< 15mins prior to dosing), 1hr ± 10mins, 1.5hr ± 10mins, 3hr ± 10mins, and 5hr ± 15mins.

6.5.2 PK urine collection

Urine sampling time points for subjects received ATG-008 at the initial doses of 15 mg, 30 mg and 45 mg/QD:

Total urine collections for PK analysis on Day -1 through Day 0 will be taken over the following times: Predose (<30 minutes prior to dosing, to completely empty the bladder), 0-4 hr and 4-8 hr and 8-24 hr.

Urine sampling time points for subjects received ATG-008 at the initial dose of 20 mg/BID:

At Day -1: 0hr (30 minutes prior to dosing), 0-4 hr, 4-8 hr and 8-12 hr after the first dose of ATG-008;

7. STUDY POPULATION

7.1 Number of Subjects

The 35 HBV+, unresectable HCC subjects who have received at least one prior line of systemic therapy have been enrolled in this study.

According to the previous study results, the sponsor plans to continue to enroll approximately 40 subjects to receive ATG-008 at an initial dose of 45mg/QD or 20 mg/BID.

If ORR of tumor is greater than 15% in the study dose group (45 mg/QD or 20 mg/BID), this study will be expanded to enroll additional approximately 110 subjects using ORR as the primary study endpoint, to further evaluate the efficacy and safety of ATG-008.

7.2 Inclusion Criteria

Subjects must meet all the following criteria to be enrolled in the study:

1. Male or female aged from 18 to 70 years (inclusive) at the time when the ICF is signed.
2. Confirmed pathologic or radiologic diagnosis of HCC according to the American Association for the Study of Liver Disease (AASLD) guidelines.
3. Unresectable stage B (intermediate) or C (advanced) HCC according to the Barcelona Clinic Liver Cancer (BCLC) staging. If stage B, the subject must have progressed after, or not be eligible for, surgical or locoregional therapy.
4. There is at least one measurable lesion according to RECIST 1.1 criteria.
5. HBV+ is defined as chronic HBV infection or a history of HBV infection, based on any of the following serologic results: HBcAb+, HBsAg+, HBV-DNA+.
6. Received at least one prior line of systemic therapy (with radiologic disease progression during or following sorafenib and/or chemotherapy). Subjects with alternative treatments such as regorafenib and/or anti PD-1 antibodies etc. approved by local health authorities are allowed to enter study if they meet all other inclusion/exclusion criteria.
    a. Chemotherapy is defined FOLFOX (fluorouracil, leucovorin and oxaliplatin), or any other platinum-containing regimen.
    b. Chemotherapy ≥ two cycles
7. ECOG performance status score of 0 or 1.
8. Serum chemistry results, evidenced by the following:
    a. AST (SGOT) and ALT (SGPT) ≤ 5x upper limit of normal range (ULN).
    b. Total bilirubin ≤ 2 x ULN.
    c. Creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 50 mL/min.
    d. Lipase and amylase ⩽2 x ULN;
9. Adequate bone marrow function, evidenced by the following:
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9 cells/L.
    b. Platelets ≥ 75 x 10^9 cells/L.

c. Hemoglobin ≥ 9 g/dL.

10. Coagulation function: international normalized ratio (INR) ≤2.0, prothrombin time (PT) ≤1.5 x ULN;

11. Child-Pugh A and B7 and hepatic encephalopathy scored as 1 point;

12. Except hearing loss and alopecia, all toxicities caused by previous anti-tumor therapies must recover to ≤ Grade 1 (based on NCI-CTCAE Version 4.03);

13. Male subjects (including those who have had a vasectomy) must agree to use a condom during sexual intercourse with females of child-bearing potential, and shall not conceive a child starting from the time of ICF signature, while on study medication, and for 3 months after the last dose of study drug.

14 Female subjects of child-bearing potential must have both of the following:

a. Agree to the use of two study physician-approved contraceptive methods simultaneously or practice complete abstinence starting at the time of ICF signature, while on study medication, and for 28 days following the last dose of study drug.

i. True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

ii. Acceptable contraceptive methods include: Oral, injectable, or implantable hormonal contraceptive; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner, together with at least one barrier method.

b. Have negative serum pregnancy test result at Screening confirmed by negative urine pregnancy test within 72 hours prior to first dose of study drug (if serum test occurred > 72 hours from first dose); pregnancy test must have a sensitivity of at least 25 mIU/mL.

7.3 Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Intolerant to sofafenib/regorafenib, e.g.:

   a. The drug is discontinued due to adverse events;

   b. The related adverse events of Grade ≥2 continued/relapsed after supportive treatment and/or dose reduction or dose interruption at least 7 days;

   c. The treatment course is less than 21 days within 28 days before discontinuation; the lowest daily dose of sorafenib is 400mg/day.

2. Medical history of hepatic encephalopathy;

3. Central nervous system metastases;

4. Treatment with molecular targeted therapies such as sorafenib, regorafenib or lenvatinib within 4 weeks before screening;

5. Treatment with locoregional HCC therapy (including but not limited to TACE, RFA), systemic chemotherapy, hormonal therapy (e.g., tamoxifen), traditional Chinese

medicine with anti-tumor effect, or clinical investigational drugs within 4 weeks prior to Screening.

6. Tested positive for both HBV and hepatitis C virus (HCV).
    a. HCV positive is defined as anti-HCV or HCV-RNA positive
7. Life expectancy of less than 3 months.
8. Prior therapy with mTOR (TORC1 and/or TORC2) inhibitors including sirolimus, temsirolimus, everolimus and other investigational or approved mTOR/PI3K/AKT inhibitors.
9. Have received major surgery within 4 weeks before screening or plan to receive major surgery during study period;
10. Receiving active, ongoing treatment with systemic corticosteroids at a prednisone equivalent dose of ≥ 10 mg daily or other systemic immune system modulators. The exceptional cases of such criterion are listed as follows:

    a. Intranasal, inhaled and topical steroids or local steroid injection (e.g., intra-articular injection);

    b. Prednisone not more than 10 mg/day or its equivalent physiological dose of systemic corticosteroids;

    c. Steroids as the prophylatic medication of allergic reactions (pretreatment before CT scan);
11. Imaging test results showing main portal venous tumor thrombus, inferior vena cava tumor thrombus or heart involvement;
12. Uncontrolled diabetes, defined as HbA1c > 7%.
13. Prior organ transplant.
14. Uncontrolled pleural effusion or pericardial effusion (with clinical symptoms, fluctuation of effusion or requiring repeated drainage, oral diuretics etc.) at screening; Ascites at screening, which can be detected by physical examination, or clinical symptoms caused by ascites, or requiring special treatment such as repeated drainage, peritoneal drug perfusion etc. (subjects who only have a small amount of ascites which can be detected by imaging examination can be enrolled).
15. Persistent diarrhea or malabsorption ≥ National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03) grade 2, despite medical management, or any significant gastrointestinal disorder that could affect the absorption of study drug.
16. Medical history of active upper gastrointestinal hemorrhage, ulcer or esophageal varices associated with hemorrhage or such diseases within 6 months;
17. Subjects who have medical history of human immunodeficiency virus infection and/or acquired immunodeficiency syndrome;
18. Concurrent active second malignancy for which the subject is receiving therapy, excluding non-melanomatous skin cancer, non-progressive prostate cancer treated with hormonal therapy, or carcinoma in situ of the cervix. Any cancer curatively treated >5 years prior to entry is permitted.
19. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection (e.g., tuberculosis) requiring antibiotic, antifungal, or antiviral therapy (other than anti-HBV therapy), acute or chronic pancreatitis or psychiatric illness/social

situations that would limit compliance with study requirements.

20. Subjects who have clinically significant cardiovascular diseases such as Grade Ⅱ and above cardiac dysfunction (New York Heart Association criteria), ischaemic heart diseases (e.g., myocardial infarction or unstable angina pectoris), clinically significant supraventricular or ventricular arrhythmia, uncontrolled hypertension (systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg), echocardiography showing ejection fraction <50%, QTc interval >450 ms (male), QTc interval >470 ms (female);
21. The subject's complications or other conditions may affect protocol compliance or make the subjects unsuitable to participate in this study at the discretion of the investigator;

8. DESCRIPTION OF STUDY TREATMENTS

8.1 Description of Investigational Product(s)

Antengene Corporation will supply ATG-008 in 15 mg, 20 mg, and 30 mg tablets; ATG-008 tablets are manufactured using conventional solid oral dosage form excipients.

Study drugs are stored at room temperature at 15-25 Celsius degree.

8.2 Treatment Administration and Schedule

The first part of this study will consist of two cohorts. Six subjects will receive a single dose of 15 mg ATG-008 on Day -1 and then receive 15 mg ATG-008 daily in 28-day cycles. Providing dose-limiting toxicity (DLT) occur in less than 2 of those 6 subjects who complete Cycle 1, 24 new subjects will receive a single dose of 30 mg ATG-008 on Day-1 and then receive 30 mg ATG-008 daily in 28-day cycles. Subjects who tolerated the 15-mg dose level may then dose-escalate to 30 mg at the Investigator's discretion.

According to the previous study results, the sponsor will plan to continue to enroll approximately 40 hepatitis B virus (HBV) positive, unresectable HCC subjects who have received at least one prior line of systemic therapy. Among which, approximately 20 subjects will receive oral ATG-008 at an initial dose of 45 mg/QD and another 20 subjects will receive oral ATG-008 at an initial dose of 20 mg/BID. The pharmacokinetic (PK) samples will be collected from 10 subjects each in the two dose groups.

Each dose of study drug will be taken at the same time each day, and can be taken with or without food. On clinic visit days, study drug will be administered in the clinic after all predose tests have been completed. Subjects should come to the clinic after fasting for 6 hours and food will be taken after all fasting tests have been completed prior to dosing.

In addition to study drug, all subjects may receive best supportive care (BSC) as determined by the Investigator according to local/institutional guidelines. Best supportive care is defined as non-specific anti-tumor treatment with the effect to maximize quality of life, including antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support and excluding surgery, TACE, RFA, immunotherapy, anticancer hormonal therapy, systemic chemotherapy, and radiotherapy (Zafar, 2008).

Treatment cycles are defined for administrative purposes as 28 days (except cycle 1).

8.2.1 Treatment modification

At the discretion of the Investigator and subject, starting with Cycle 3, Day 2, dosing may be moved to the end of the day to manage AEs (e.g. gastrointestinal).

8.2.1.1 Treatment Delay

Study drug may be taken up to 12 hours late if dosing has been delayed on a single day; otherwise that day's dose should be omitted and dosing continue on the following day. The subject should never take more than the scheduled dose on any single day.

If study drug is interrupted for more than 21 consecutive days, treatment should be permanently discontinued unless agreed in advance with Antengene.

8.2.1.2 Dose Adjustments

Dosing may be reduced or interrupted for toxicities according to Table 4. Dose adjustments are to be made according to the AE showing the greatest degree of toxicity. Toxicities will be graded using the NCI CTCAE v4.03.

If considered necessary, the dose of ATG-008 should be reduced from 30 mg/d to 20 mg/day, as the first dose reduction level. If a second dose reduction is considered necessary, the ATG-008 dose should be reduced to 15 mg/day.

Continuous dose interruption of up to 2 weeks and the total discontinuation time not more than 4 weeks is allowed in this study.

Dose reduction principle for subjects who are enrolled to receive oral ATG-008 at an initial dose of 45 mg/QD or 20 mg/BID: 45 mg/QD can be reduced to 30 mg, 20 mg, 15 mg/QD; 20 mg/BID can be reduced to 15mg/BID or other doses so as to mitigate toxicity. If further dose reduction is required, it can be implemented according to the considerations of the investigator and discussion between the investigator and medical monitors of the sponsor. Dose re-escalation (higher than the initial dose is not permitted) will be allowed if the same toxicity does not recur at the reduced dose for least one cycle (4 weeks).

The dose reduction guidelines listed in Table 4 below are recommended to be used for dose modifications.

Table 4: Dose Reduction Recommended Guidelines for Suspected Drug-related Toxicity

Adverse Event	Grade	Action
Thrombocytopenia	3	If bleeding present, reduce study drug one dose level.
	4	If present for more than 7 days, hold study drug until ≤ grade 2. Then reduce study drug one dose level.
Neutropenia	3	If associated with fever, reduce study drug one dose level.
	4	If present for more than 7 days or associated with fever, hold study drug until ≤ grade 2. Then reduce study drug one dose level.
Increased bilirubin	3	If > 5 x ULN, hold study drug until ≤ grade 2. Then reduce study drug one dose level.
	4	Hold study drug until ≤ grade 2. Then reduce study drug one dose level.
Transaminase increase	3	If > 10 x ULN, hold study drug until ≤ grade 2. Then reduce study drug one dose level.
	4	Hold study drug until ≤ grade 2. Then reduce study drug one dose level.
Stomatitis / mucositis / vomiting / diarrhea	3	If unable to control with optimal medical management within 7 days, reduce study drug one dose level.
	4	Hold study drug until ≤ grade 2. Then reduce study drug one dose level.
Hyperglycemia	3 or 4	If unable to control with optimal medical management within 7 days, reduce study drug one dose level. Management guidelines provided in Appendix C (Section 19.3).

Rash	3	If fails to respond to optimal medical management within 7 days, hold study drug until ≤ grade 2. Then reduce study drug one dose level.
	4	Discontinue study drug.
Pneumonitis	1	Continue study drug and monitor closely.
	2	Hold study drug until ≤ grade 1. Then maintain or reduce study drug one dose level.
	3 or 4	Discontinue study drug.
Fatigue	3	If fails to respond to optimal medical management within 7 days, hold study drug until ≤ grade 2. Then reduce study drug one dose
Other	3	Reduce study drug one dose level.
	4	Discontinue study drug.

8.2.2 Overdose

On a per dose basis, an overdose is defined as any amount over the protocol-specified dose of study drug assigned to a given subject, regardless of any associated adverse events or sequelae. On a frequency basis, an overdose is defined as anything more frequent than the protocol required frequency.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form. See Section 11.1 for the reporting of adverse events associated with overdose.

8.3 Method of Treatment Assignment

Subjects who are in the first part of this study and are enrolled into screening period of will be assigned with one available subject number The assignment to cohort of 15mg or 30mg will be in sequence.

As for approximately 40 HCC subjects who are planned to be enrolled, subjects will be randomly assigned with one available subject number during screening period to receive oral ATG-008 at an initial dose of 45 mg/QD or 20 mg/BID.

8.4 Packaging and Labeling

ATG-008 are packaged in bottles. The study drug will be labeled per local regulations.

8.5 Investigational Product Accountability and Disposal

Antengene (or designee) will review with the Investigator and relevant site personnel the process for Investigational Product return, disposal, and/or destruction including responsibilities for the site vs. Antengene (or designee).

Investigational product containers that are returned should be retained by the site until a representative from Antengene or other Antengene-designated personnel have completed an inventory, unless otherwise agreed with Antengene. Completely used containers should be destroyed according to local guidelines, and disposition should be recorded on the Investigational Drug Accountability Record Form.

The Investigator, or a designee, shall record the dispensing of study drug to subjects in the study drug accountability record. The study drug record will be made available to Antengene, or other authorized Antengene-designated monitoring personnel for the purpose of accounting for the study drug supply. Inspections of the study drug supply for inventory purposes and assurance of proper storage will be conducted as necessary. Any significant discrepancy will be recorded and reported to Antengene or a designee and a plan for resolution will be

documented.

Investigational product will not be loaned or dispensed by the Investigator to another Investigator or site. Under certain circumstances, and with Antengene permission, cooperative groups may manage investigational product between locations within their network as clinical trial agreement and local guidelines permit.

8.6 Investigational Product Compliance

Accurate recording of all study drug administration will be made in the appropriate section of the subject's case report form (CRF) and source documents. The Investigator or designee is responsible for accounting for all study-specific study drug either administered or in their custody during the course of the study.

9. CONCOMITANT MEDICATIONS AND PROCEDURES

9.1 Recommended Concomitant Medications and Procedures

Antiviral therapy can reduce the risk of developing HCC, decrease the risk of HBV reactivation, reduce the recurrence, and improve OS and DFS of HCC patients (Ge, 2015). Therefore, antiviral therapy is required for all subjects with chronic HBV infection manifested by positive HBcAb IgM or total, positive HBsAg or HBeAg, or positive DNA-HBV viral load, or according to local practice. Standard treatment options may include entecavir, tenofovir, or telbivudine, recommended by Clinical Practice of Primary Liver Cancer 2017 (NFHPC, 2017). Lamivudine is not recommended due to higher rates of resistance in subjects with active HBV infection (HBsAg+, HBeAg+, viral load positive). Continued antiviral therapy is recommended for at least 6 months following completion of study drug treatment, or as required by local practice.

9.2 Permitted Concomitant Medications and Procedures

Over the course of this trial, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from trial treatments or disease progression. In general, the use of any concomitant medication/therapies considered necessary for the care of the subject is permitted.

Prophylactic antiemetics are not required. If nausea and vomiting develop, the subject may then receive antiemetics at the discretion of the treating physician.

Stable, therapeutic doses of anticoagulants are permitted; however subjects on warfarin should have PT/INR/PTT monitored as clinically indicated.

Subjects receiving recombinant erythropoietin or darbepoetin alfa for at least 4 weeks prior to starting the study drug may continue their pretreatment doses throughout the trial.

Parenteral flu vaccination is permitted.

Anti-diabetic drugs (e.g., biguanides, insulin) are recommended to control drug-induced hyperglycemia. It is recommended that biguanides (e.g., metformin) be held 12 hours prior to and 48 hours following intravascular administration of iodinated contrast media because of their potential for acute alteration in renal function.

Treatment-related rash should be treated according to standard medical practice and Investigator judgment. Careful descriptions should be documented to help determine the nature of the rash later classification of the rash. Depending on the severity and type of rash, specific treatments may need to be administered, and study drug may need to be withheld temporarily or permanently (as described in Table 4). Treatments for rash may include non-occlusive moisturizers, topical or systemic antihistamines (e.g.,

diphenhydramine), and/or corticosteroids (with appropriate consideration to the risk of hyperglycemia). Superinfections should be cultured and appropriate topical or systemic antibiotic therapy considered.

Treatment-related mucositis and mouth ulcers should be treated as early as possible and according to standard medical practice and Investigator judgment. This may include analgesics, topical preparations (suspensions, pastes), and short courses of systemic steroids with temporary dose interruption and/or dose reduction for more severe cases. Alcohol or peroxide-containing mouthwashes should be avoided.

Acute renal insufficiency has been reported with ATG-008 and other agents in this drug class. Typically, this has been associated with drug-related gastrointestinal toxicities (anorexia, nausea, vomiting, diarrhea, mucositis) leading to dehydration and electrolyte abnormalities. Treatment with rehydration, antiemetics, and antidiarrheals is recommended, as medically indicated. Study drug dose adjustments may be used to manage these toxicities.

Drug-related pancreatitis including asymptomatic amylase and lipase elevations, as well as symptomatic pancreatitis, has been reported with ATG-008 as with other drugs in this class. Routine amylase and lipase safety lab monitoring is included in the protocol. It is recommended that subjects with symptoms of clinical pancreatitis including abdominal pain, nausea and vomiting be managed with bowel rest and pain management as medically indicated. study drug dose adjustments may be used to manage these toxicities.

Drug-related noninfectious pneumonitis, a class effect of drugs targeting the mTOR pathway, has been reported with ATG-008. The diagnosis should be considered in subjects presenting with non- specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, dyspnea, or interstitial pulmonary infiltrates, and in whom infectious, neoplastic and other causes are excluded by appropriate investigations. Those with radiological features suggestive of non- infectious pneumonitis but with minimal symptoms may continue study drug without dose alteration. Moderate symptoms may require interrupting therapy, and corticosteroids may be indicated. Once symptoms have resolved, study drug may be reintroduced at the assigned or a reduced dose level, depending on the subject's general clinical status. For severe symptoms, study drug should be discontinued and corticosteroids used until clinical symptoms have resolved.

Routine infectious disease prophylaxis (other than for HBV infection as described in Section 9.1) is not recommended. However, antibiotic, antiviral, antipneumocystis, antifungal, or other prophylaxis may be implemented during the trial at the discretion of the Investigator.

Treatment with bisphosphonates (e.g., pamidronate, zolendronate), or other agents (e.g., denosumab) to prevent or delay progression of bone metastases is permitted. Maintenance of a stable dosing regimen throughout the study is recommended.

Subjects may receive physiologic replacement doses of glucocorticoids (up to the equivalent of 10 mg daily prednisone) as maintenance therapy for adrenal insufficiency.

All concomitant treatments (treatment or prevention purpose), including blood and blood products, must be reported on the CRF.

9.3 Prohibited Concomitant Medications and Procedures

Administration of other chemotherapy, immunotherapy, antitumor hormonal therapy, other investigational therapy or other anticancer therapy during the treatment period is not allowed. Focal palliative radiotherapy or surgical intervention for non-target lesions for treatment of cancer-related symptoms is allowed during trial treatment at the discretion of the Investigator. TACE is not allowed during clinical trial treatment period. Surgical intervention

or radiation of target lesions followed for RECIST 1.1 during this trial will require discontinuation of the subject from trial treatment.

Traditional herbal or Chinese medicine for cancer (e.g., Minor Bupleurum Decoction [xiao chai hu tang] and cinobufagin [hua chan su]) is not permitted while on trial treatment and should be stopped prior to the first dose date.

Routine prophylaxis with granulocyte-colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) is not allowed. These should be used with therapeutic intent and only when indicated, according to standard medical practice and Investigator judgment.

The administration of α-interferon is prohibited during trial treatment.

In vitro metabolism studies demonstrated that oxidative metabolism of ATG-008 is primarily catalyzed by CYP3A4/5, and to a limited extent CYP2C9. Hence concomitant potent CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir) and inducers (e.g., rifampicin, phenobarbital, phenytoin, carbamezepine) are better avoided during treatment with study drug when possible. Foods and beverages containing grapefruit may be allowed. A list of common medications belonging to these classes is shown in Appendix B, Sections 19.2.1 and 19.2.2.

Medications metabolized by CYP3A4/5 and CYP2C9 may be administered in this trial but subjects must be monitored for drug interactions and potentiation of toxicity. All such medication must be recorded on CRFs, including dose and dose frequency.

In vitro studies demonstrate that ATG-008 may be a moderate activator of pregnane X receptor and moderate inducer of CYP3A4/5. The in vivo magnitude of the ATG-008 induction is unknown but it might reduce the clinical effectiveness of oral or injectable contraceptives. For this reason double contraceptive methods must be used throughout the trial by fertile subjects.

9.4 Required Concomitant Medications and Procedures

See Section 9.1 for details. In addition, all subjects may receive BSC as clinically indicated.

10. STATISTICAL ANALYSES

10.1 Overview

This is an Asian multi-regional clinical trial (MRCT) in which ATG-008 will be administered orally to hepatitis B positive (HBV+) HCC subjects who have received at least one prior line of systemic therapy.

According to the previous study results, the sponsor will plan to continue to enroll approximately 40 hepatitis B virus (HBV) positive, unresectable HCC subjects who have received at least one prior line of systemic therapy. Among which, approximately 20 subjects will receive oral ATG-008 at an initial dose of 45 mg/QD and another 20 subjects will receive oral ATG-008 at an initial dose of 20 mg/BID. The pharmacokinetic (PK) samples will be collected from 10 subjects each in the two dose groups so as to further evaluate the PK profile of ATG-008 and its metabolites.

If ORR of tumor is greater than 15% in the study dose group (45 mg/QD or 20 mg/BID), this study will be expanded to enroll additional approximately 110 subjects using ORR as the primary study endpoint, to further evaluate the efficacy and safety of ATG-008.

It is designed as an open-label phase 2 trial evaluating the pharmacokinetics (PK), tolerability and efficacy of oral ATG-008 administered daily until the radiologic disease

progression (according to RECIST 1.1) or intolerable toxicity.

The sections below provide an overview of the proposed statistical considerations and analyses. The final statistical analysis methods will be documented in detail in the Statistical Analysis Plan (SAP).

10.2 Study Population Definitions

10.2.1 Treated Population

The Treated population will consist of all enrolled subjects who received at least one dose of study drug. It is equivalent to the Safety population. The Treated population will be used for the primary efficacy and safety analyses for this single arm Phase 2 study. Treated population will be used (instead of Safety population) for the rest of the protocol.

10.2.2 Per-Protocol Population

The per-protocol population consists of all treated subjects who met all eligibility criteria and received at least 80% of doses during Cycle 1, and have at least one postbaseline tumor assessment. The primary and secondary efficacy endpoints will also be analyzed based on the Per-protocol population and considered as supportive for this study.

10.3 Sample Size and Power Considerations

For the primary efficacy endpoint, ORR, the sample size is based on one-sample binomial test with normal approximation. The null hypothesis to be tested is that the ORR (defined as the proportion of subjects with at least a partial response (PR) based on the Treated population subjects) is ≤10%; the alternative hypothesis is that the ORR is ≥ 18%. With these hypotheses, a sample size of 130 (20+110) subjects in the Treated population would provide 80% power at a one-sided 0.025 significance level. This criterion requires that the lower limit of the 95% confidence interval (CI) for the ORR is greater than 10%.

10.4 Background and Demographic Characteristics

Subject age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations.

Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

Background, demographic characteristics, and medical history will be summarized using both Treated and per-protocol populations.

10.5 Subject Disposition

Subject disposition (analysis population, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

Subject disposition and protocol deviations will be summarized using both Treated and per-protocol populations.

10.6 Efficacy Analysis

All efficacy results will be summarized for the Treated population as the primary analysis. The primary and secondary efficacy endpoints will also be analyzed using the per-protocol population as supportive analysis. Subgroup and exploratory efficacy analyses will be conducted using only the Treated population.

10.6.1 Analysis of the Primary Efficacy Endpoint

Overall response rate (ORR) is the primary efficacy endpoint. A responder is any subject who achieves a CR or PR. ORR is defined as the percentage of subjects that achieve a CR or PR.

ORR will be summarized with 95% confidence interval (CI), and tested using one sample binomial test for the Treated population analyzed in a similar way as for DCR. Subgroup analysis for ORR will be performed for subgroups specified in Section 10.6.3.

ORR with 95% confidence intervals will also be provided for the per-protocol population.

The primary analysis for ORR will be performed at approximately 3 months after the last subject is first dosed. All other endpoints will be analyzed at the same time. The analysis will be updated at 12 months after the last subject's first dose date.

10.6.2 Analysis of the Secondary Efficacy Endpoints

Overall Survival is defined as the time from the first dose date until death. A subject who has not been reported as a death will be censored at the last available date the subject is known to be alive, or the clinical cut-off date, whichever is earlier.

Time to progression (TTP) will be calculated as the time from the first dose date to disease progression. Subjects who do not have disease progression will be censored at the date of the last tumor assessment that the subject was progression free, or the clinical cutoff date, whichever is earlier.

Progression free survival (PFS) is defined as the time from the first dose date to the date of disease progression according to RECIST 1.1 or death (due to any cause) on or prior to the clinical cutoff date, whichever occurs earlier. Subjects who do not have disease progression or have not died will be censored at the date of the last tumor assessment that the subject was progression free on or prior to the clinical cutoff date.

Disease control rate (DCR) is defined as the percentage of subjects with complete (CR), or partial response (PR) or stable disease (SD).

For responders, time to response (TTR) and response duration will be analyzed.

TTR is the time from the first dose date to the first documentation of response of PR or better. TTR will be summarized for responders using summary statistics.

Duration of response (DOR) is defined as the time from the time when criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented for responders. DOR will be censored using the same censoring rules as used for PFS.

Survival rate is defined as the Kaplan-Meier estimated proportion of subjects surviving at 6, 9, 12 months.

10.6.3 Subgroup Analyses

The effect of treatment on the efficacy variable ORR, OS, PFS, TTP and DCR will be investigated within subgroups defined by the following baseline prognostic variables if the study is expanded:

- Age group (≤ 65, > 65 years);
- Baseline ECOG Performance Status (0 or 1);
- Macroscopic vascular invasion (involvement of branches of portal or hepatic veins: yes or no);
- Extrahepatic spread (yes or no);

- Median baseline level of albumin (> median or ≤ median);
- Median baseline level of alkaline phosphatase (> median or ≤ median);
- Median baseline level of total bilirubin (> median or ≤ median);
- Prior systemic therapy (First line or more than first-line)
- Portal vein thrombosis (yes or no);
- AFP (≤400ug/L or >400ug/L)
- Liver involvement by HCC (≤50% or >50%)
- BCLC Stage (B or C);

The analysis methods described in previous sections will be used for each subgroup separately. A forest plot for subgroups will be also provided for the primary efficacy endpoint ORR.

10.6.4 PK analysis

Intensive PK modeling will be performed for ATG-008 and M1 on the plasma and urine concentration data. Descriptive statistics of model fitting and PK parameters will be summarized in appropriate tables and figures.

10.6.5 Exploratory Analyses

10.6.5.1 Evaluate Changes in AFP

An AFP response is defined as normalization or > 50% decline from baseline. The AFP response rate is the percentage of subjects with baseline elevation in AFP who meet AFP response criteria. The response rate will be summarized descriptively.

10.6.5.2 Exposure-Response Analyses

Exploratory analyses may be conducted to evaluate the relationship between ATG-008 and M1 exposure and select response variables. Graphical exploration may initially be performed to identify significant trends between drug exposure and response. Depending on the findings, appropriate modeling and simulation may be conducted to quantify exposure-response relationships using pharmacostatistical modeling.

10.7 Safety Analysis

All safety results will be summarized for the Safety population.

Safety and tolerability will be monitored through continuous reporting of adverse events and serious adverse events, laboratory abnormalities, and incidence of subjects experiencing dose modifications, dose interruptions, and/or premature discontinuation of study drug. Data from all subjects who receive one or more doses of study drug will be included in the safety analyses. Adverse events, physical examination findings (including vital sign measurements), clinical laboratory information, ECG interpretations and concomitant medications/procedures will be tabulated and summarized by treatment arm. Descriptive statistics will be provided for both baseline and change from baseline of ECG values by treatment arm. All toxicities will be summarized by severity grade based on the CTCAE, Version 4.03, frequency and relationship to treatment. Adverse events will be coded according to the Medical Dictionary for Regulatory Affairs (MedDRA). Serious adverse events, AEs of interest, AEs Grade 3 or higher, and AEs leading to discontinuation or death will be summarized and listed separately.

11. ADVERSE EVENTS

11.1 Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a trial. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concurrent impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 11.3), regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Clinically significant signs and symptoms associated with disease progression are expected to be reported as AEs; however progression of HCC (PD) that is asymptomatic or solely documented radiographically per RECIST 1.1 does not require reporting as an AE.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms. See Section 8.2.2 for the definition of overdose. In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for ATG-008 overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the trial. Assessments may include monitoring of any or all of the following parameters: The subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs and SAEs will be recorded by the Investigator from the time the subject signs informed consent to 28 days after the last dose of study drug. However serious adverse events made known to the Investigator at any time thereafter that are suspected of being related to study drug will also be reported. AEs and serious adverse events (SAEs) will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Antengene Drug Safety or designee within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

11.2 Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

11.2.1 Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;

- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events not considered to be SAEs are hospitalizations for:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion is a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures is a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on trial); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication from such a procedure is a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to study drug, action taken regarding study drug, and outcome.

For death caused by study indication progression of disease (PD) will not be reported as SAE.

11.2.2 Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of CTCAE, Version 4.03;

Adverse events that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible

- Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

11.2.3 Causality

The Investigator must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: A causal relationship of the adverse event to study drug administration is unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: There is a reasonable possibility that the administration of study drug caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the study drug and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional study drug that has not been manufactured or provided by Antengene, then the name of the manufacturer when reporting the event will be provided.

11.2.4 Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

11.2.5 Action Taken

The Investigator will report the action taken with study drug as a result of an AE or SAE, as applicable (e.g., discontinuation or reduction of study drug, as appropriate) and report if concomitant and/or additional treatments were given for the event.

11.2.6 Outcome

The Investigator will report the outcome of the event for both AEs and SAEs. All SAEs that have not resolved upon discontinuation of the subject's participation in the trial must be followed until recovered, recovered with sequelae, not recovered or death (due to the SAE).

11.3 Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- Results in discontinuation from the trial;
- Requires treatment, modification/interruption of study drug dose, or any other therapeutic intervention; or
- Is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion

need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (e.g., record thrombocytopenia rather than decreased platelets).

11.4 Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject or partner of a male subject are immediately reportable events.

11.4.1 Females of Childbearing Potential

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study drug, or within 28 days of the subject's last dose of study drug, are considered immediately reportable events. study drug is to be discontinued immediately and the subject instructed to return any unused portion of the study drug to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Antengene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject may be referred to an obstetrician-gynecologist or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy and must notify Antengene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Antengene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the study drug should also be reported to Antengene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

11.4.2 Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant up to 3 months after stopping study drug, the male subject taking study drug should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

11.5 Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Antengene Drug Safety designee within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to study drug) that occur during the trial (from the time the subject signs informed consent to 28 days after the last dose of study drug), and those made known to the Investigator at any time thereafter that are suspected of being related to study drug. Serious adverse events occurring prior to treatment (after signing the ICF) will be captured. SAEs should be followed to resolution.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Antengene Drug Safety as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Antengene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Antengene and the IRB/EC.

11.5.1 Safety Queries

Queries pertaining to SAEs will be communicated from Antengene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (e.g., missing causality assessment) may be handled by phone.

11.6 Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Antengene Drug Safety will determine the expectedness of events suspected of being related to study drug based on the Investigator Brochure.

All SUSARs will be reported in an expedited manner in accordance with 21 CFR 312.32.

For participating Asian countries, Antengene or an authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, SUSARs in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Adverse events such as disease progression, death related to disease progression (in the absence of serious study drug-related events) and serious events due to the relapse of the studied indication will not be subject to expedited reporting by Antengene to regulatory authorities.

Antengene or an authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of study drug in this trial or in other studies that is both serious and unexpected (i.e., SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Antengene and the IRB/EC. (See Section 15.3 for record retention information).

Antengene Drug Safety Contact Information:

For Antengene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines

12. DISCONTINUATIONS

12.1 Discontinuation from Investigational Product

The following events are considered sufficient reasons for discontinuing a subject from the study drug:

- Adverse Event(s) (that are intolerable)
- Disease progression
- Symptomatic deterioration (global deterioration of health status)
- Physician decision
- Withdrawal by subject (from treatment only)
- Death
- Lost to follow up
- Protocol violation
- Other (to be specified on CRF)

The reason for treatment discontinuation should be recorded in the CRF and in the source documents. Subjects will continue to be followed for post-treatment anticancer therapy and survival status until death.

12.2 Discontinuation from the Trial

The following events are considered sufficient reasons for discontinuing a subject from the trial:

- Death
- Protocol violation
- Lost to follow-up
- Withdrawal of consent for post-treatment follow-up
- Other (to be specified on CRF)

The reason for trial discontinuation should be recorded in the CRF and in the source documents.

At the time of withdrawal, it should be determined if the subject is withdrawing from treatment alone, or from treatment and collection of further data (e.g., survival).

13. EMERGENCY PROCEDURES

13.1 Emergency Contact

In emergency situations, the Investigator should contact the responsible physician at the number listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the physician cannot be reached, the Emergency Center should be contacted at the number listed. The Emergency Call Center is open 24 hours a day and 7 days a week. The representatives there are responsible for contacting an alternative on-call Antengene/CRO Medical Director, who will then assist the enquirer promptly.

The back-up 24-hour emergency contact call center should only be used in the event that the physician cannot be reached.

14. REGULATORY CONSIDERATIONS

14.1 Good Clinical Practice

The procedures set out in this trial protocol pertaining to the conduct, evaluation, and documentation of this trial are designed to ensure that Antengene, an authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The trial will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this trial in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

14.2 Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Antengene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, amendments, trial treatments, as well as study-related duties and functions. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an ICF and are screened for entry into the trial. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

14.3 Subject Information and Informed Consent

The Investigator must obtain informed consent of a legal representative prior to any study-related procedures.

Documentation that IC occurred prior to the study subject's entry into the trial and of the informed consent process should be recorded in the subject's source documents including the date. The original ICF signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's trial files and a copy given to the subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. S ubjects participating in the trial when the amended protocol is implemented must be re- consented with the revised version of the ICF. The revised ICF signed and dated by the subject and by the person consenting the subject must be maintained in the Investigator's trial files and a copy given to the subject.

14.4 Confidentiality

Antengene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Antengene requires the Investigator to permit Antengene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the trial in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

14.5 Protocol Amendments

Any amendment to this protocol must be approved by the Antengene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

14.6 Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the trial, the protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

Study drug can only be supplied to an Investigator by Antengene or an authorized representative after documentation on all ethical and legal requirements for starting the trial has been received by Antengene or an authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list.

Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the trial, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and

regulatory authorities.

Any advertisements used to recruit subjects for the trial must be reviewed by Antengene and the IRB/EC prior to use.

14.7 Ongoing Information for Institutional Review Board / Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the trial;
- Deviations from the protocol or anything that may involve added risk to subjects.

14.8 Closure of the Trial

Antengene reserves the right to terminate this trial at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

In addition, the Investigator or Antengene has the right to discontinue a single site at any time during the trial for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the trial protocol.

15. DATA HANDLING AND RECORDKEEPING

15.1 Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the trial and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: Hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film/tumor scans and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

15.2 Data Management

Data will be collected via CRF and entered into the clinical database per Antengene or an authorized representative's standard operating procedures (SOPs). These data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

15.3 Record Retention

Essential documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the ATG-008. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICF for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Antengene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the trial, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- Trial drug accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records,

etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

Investigators must notify Antengene if they wish to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Antengene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Antengene for permission to make alternative arrangements. Details of these arrangements should be documented.

All trial documents should be made available if required by relevant health authorities. Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

16. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the trial will be carefully monitored by Antengene or an authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

16.1 Trial Monitoring and Source Data Verification

Antengene ensures that appropriate monitoring procedures are performed before, during and after the trial. All aspects of the trial are reviewed with the Investigator and the staff at a trial initiation visit and/or at an Investigator meeting. Prior to enrolling subjects into the trial, a Antengene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other trial documentation will be inspected/reviewed by the Antengene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

16.2 Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Antengene. Representatives of this unit will conduct audits of clinical research activities in accordance with Antengene or its authorized repreentative's SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the trial took place, source documents, CRFs and applicable supporting records of trial subject participation for audits and inspections by IRB/IECs, regulatory authorities (e.g., China Food and Drug Administration, Taiwan Food and Drug Administration, Korea Food and Drug Administration) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. When Investigators are contacted by any

regulatory authority regarding an inspection, they should contact Antengene immediately.

17. PUBLICATIONS

Antengene will publish the results of this trial in a peer-reviewed medical publication, journal, or findings may also be used for teaching purposes. Additionally, this trial and its results may be submitted for inclusion in all appropriate health authority trial registries, as well as publication on health authority trial registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to, trial participation, subject enrollment, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a trial.

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19. APPENDICES

19.1 Appendix A: RECIST 1.1

The following information is extracted/summarized from Eisenhauer 2009, New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Please refer to the primary reference for further information.

19.1.1 Definitions

At screening, tumor lesions/lymph nodes will be categorized as measurable or non-measurable.

19.1.1.1 Measurable Disease

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

19.1.1.2 Non-measurable Disease

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

19.1.1.3 Special Considerations for Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local (radiation) therapy should be considered measurable or non-measurable according to Eisenhauer, 2009.

19.1.2 Tumor Response Evaluation

19.1.2.1 Target Lesions

When more than one measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the measurable criterion of a short axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short

axis < 10 mm are considered non-pathological and should not be recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are considered to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

19.1.2.2 Non-target Lesions

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present", "absent" or "unequivocal progression".

19.1.2.3 Response Criteria

Target and non-target lesions are evaluated for response separately, and then the tumor burden as a whole is evaluated as the Overall response.

19.1.2.3.1 Target Lesion Response

Target lesions will be assessed as follows:

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): 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.)

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

19.1.2.3.2 Non-target Lesion Response

Non-target lesions will be assessed as follows:

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression.)

When the patient also has measurable disease: In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease: This circumstance arises in some Phase 3 trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden.

Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

19.1.2.3.3 Overall Response

Overall response should be assessed according to Table 5 for subjects with target lesions, and Table 6 for subjects with only non-target lesions.

Table 5: Time Point Response: Patients With Target (± Non-target) Disease

Target lesions response	Non-target lesion response	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/ non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable

Table 6: Time Point Response: Subjects With Non-target Disease Only

Non-target lesions response	New lesions	Overall response
CR	No	CR
Non-CR/ non-PD	No	Non-CR/ non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE =inevaluable

[a] 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

19.1.2.4 Symptomatic Deterioration

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease.

19.2 Appendix B: Cytochrome P-450 (CYP) interactions

A sample list of CYP450 inhibitors and inducers are provided. This list is not intended to be exhaustive, and the prescribing information of the concomitant medication should be consulted if the status is unclear. Additionally, a website such as www.drug-interaction.com could be consulted, if appropriate.

19.2.1 CYP3A4 Inhibitors

Source: Cytochrome P450 Drug Interaction Table (Flockhart, 2007)

Amiodarone	Indinavir
Aprepitant	Itraconazole
Chloramphenicol	Ketoconazole
Cimetidine	Mibefradil
Ciprofloxacin	Mifepristone
Clarithromycin	Nefazodone
Delaviridine	Nelfinavir
Diethyldithiocarbamate	Norfloxacin
Diltiazem	Ritonavir
Erythromycin	Saquinavir
Fluconazole	Star fruit
Fluvoxamine	Telithromycin
Gestodene	Verapamil

Grapefruit juice	Voriconazole
Imatinib	

19.2.2 CYP3A4 Inducers:

Source: Cytochrome P450 Drug Interaction Table (Flockhart, 2007).

(EIAED are marked with asterisks)

Barbiturates*	Phenobarbital*
Carbamazepine*	Phenytoin*
Efavirenz	Pioglitazone
Glucocorticoids	Primidone*
Modafinil	Rifabutin
Nevirapine	Rifampin
Oxcarbazepine	St. John's wort

19.3 Appendix C: Guidance for Managing Hyperglycemia

Hyperglycemia is a potential class effect of drugs inhibiting mTOR signaling pathways (Sankhala, 2009). Consequently, this protocol requires close monitoring and early intervention for hyperglycemia.

To detect meaningful incipient hyperglycemia, in Cycle 1 careful review of blood glucose results and possible hyperglycemic symptoms are need during the routine weekly clinic visits. Subjects must also be instructed how to contact study staff immediately in the event of symptoms (eg, polyuria, thirst), in which case prompt assessment in the clinic is necessary.

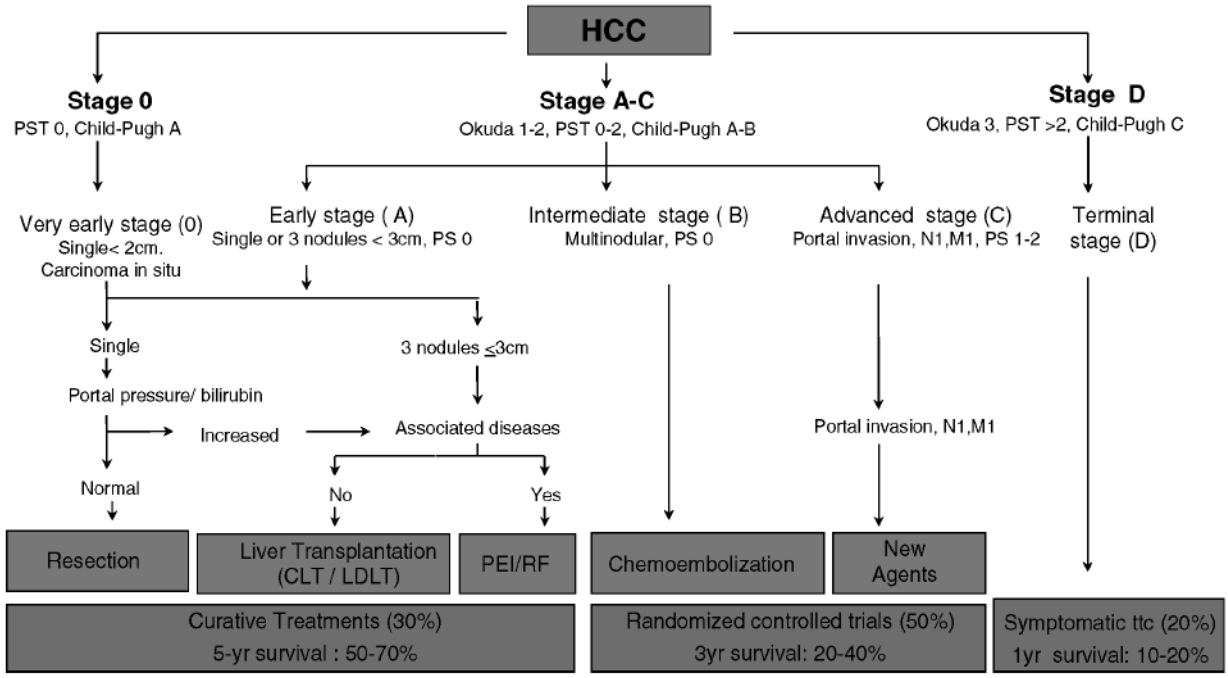
In the event of modest or intermittent hyperglycemia, more frequent monitoring may be required. In the event of persistent fasting hyperglycemia (> 126 mg/dL), or at any time considered appropriate by the Investigator, it is recommended that oral hypoglycemic therapy be initiated. Metformin hydrochloride 464 mg PO nocte is an appropriate starting therapy. It is recommended that dosage be increased by 464 mg every 3 days (or slower in the event of gastrointestinal or other intolerance) to a maximum of 2000 mg. Glucophage, and other biguanide therapy, should be temporarily suspended when planned radiological tumor assessments (e.g., CT scan) involve iodinated contrast (see Section 6.4.1). Subjects should be instructed on how to recognize hypo- and hyperglycemia. Treatment interruptions of > 3 weeks will necessitate removal of the subject from this study.

Goldberg, 2004; Goldberg, 2005; and Turina, 2006 are suggested resources for hyperglycemia management.

19.4 Appendix D: Liver Cancer Staging, and Child-Pugh Classification

19.4.1 Barcelona Clinic Liver Center Staging

Figure 2: Barcelona-Clinic Liver staging classification and treatment schedule



BCLC = Barcelona-Clinic Liver staging classification and treatment schedule.
Note: From Pons, 2005 adapted from Llovet., 2003.

19.4.2 Child-Pugh Classification of Liver Failure

Subjects with Child-Pugh A and B7 and hepatic encephalopathy scored as 1 point meet this individual inclusion criterion for the study.

Table 7: Child-Pugh Classification

	1 point	2 points	3 points
Bilirubin (mg/dL)	< 2	2-3	> 3
Albumin (g/L)	> 3.5	2.8-3.5	< 2.8
Prothrombin time prolonged in seconds (INR)	1-4 (< 1.7)	4-6 (1.7-2.3)	> 6 (> 2.3)
Ascites	None	Slight	Moderate
Hepatic encephalopathy	None	Grade 1-2	Grade 3-4
Child A: 5-6 points; Child B; 7-9 points; Child C: ≥ 10 points			

Source: Pugh, 1973