CLINICAL STUDY PROTOCOL

Protocol Title: A Phase 2 Multi-center, Open-label Study of Oral ENMD-2076 for the Treatment of Patients with Advanced Fibrolamellar Carcinoma (FLC)

Protocol Number 2076-CL-006
IND # 123,973

Study Product:	ENMD-2076
Indication:	Fibrolamellar Carcinoma
Phase:	II
Name and Affiliation of Principal Investigator:	Ghassan K. Abou-Alfa, MD. Memorial Sloan Kettering Cancer Center
Name and Address of Sponsor:	Rong Chen, MD, PhD Chief Medical Officer CASI Pharmaceuticals, Inc. 9620 Medical Center Drive, Suite 300 Rockville, MD 20850
GCP Statement:	This study will be performed in compliance with GCP, including the archiving of essential documents.

1. SYNOPSIS

TITLE: A Phase 2 Multi-center, Open-label Study of Oral ENMD-2076 for the Treatment of Patients with Advanced Fibrolamellar Carcinoma (FLC)

INVESTIGATIONAL PRODUCT: ENMD-2076

INDICATION: Fibrolamellar Carcinoma

PHASE OF DEVELOPMENT: II

INVESTIGATIONAL SITES/LOCATIONS: Multi-centers, a list of investigators and affiliated investigational sites/locations is maintained in the trial master file

OBJECTIVES:

Primary Objective:

- To determine the Overall Response Rate (ORR) using RECIST v 1.1 criteria when patients with advanced fibrolamellar carcinoma (FLC) are treated with daily oral ENMD-2076

Secondary Objectives:

- To evaluate the 6-month Progression Free Survival (PFS6) rate when patients with FLC are treated with daily oral ENMD-2076.
- To evaluate the median Progression Free Survival (PFS), Time to Progression (TTP), and Overall Survival (OS).
- To determine the safety of ENMD-2076 as defined by the frequency and severity of adverse events when patients with FLC are treated with daily oral ENMD-2076.
- To explore biomarkers predictive of tumor response to ENMD-2076 in FLC patients.

STUDY DESIGN: This is a Phase 2 study in 29 patients with advanced FLC. Primary efficacy analysis will be based on overall response rate using RECIST v 1.1 criteria. Secondary endpoints will include 6-month progression free survival rate, median PFS, TTP, and OS and the evaluation of safety.

Patients will be given an oral, daily dose of ENMD-2076 based on body surface area. In case of adverse events, two dose reductions at the discretion of the investigator will be allowed for each patient. If adverse events resolve, the dose can be increased in 50 mg increments as tolerated. Dosing interruptions/delays will be allowed at the discretion of the investigator for recovery from adverse events or inter-current illness, particularly if the patient is benefiting from therapy with ENMD-2076. After a treatment interruption for adverse events, treatment can be resumed at a lower dose and increased in 50 mg increments as tolerated.

Tumor measurements will occur every two months (± 1 week) after initial study drug administration. The overall response rate will be determined based on RECIST v 1.1 criteria. Survival and time to progression will be determined as the time from first study drug administration until death from any cause or documented progression. Patients who discontinue therapy for any reason other than progression will continue to receive imaging until progression or death.

An interim analysis will be conducted after 16 patients will have reached study endpoints of responses per RECIST 1.1 criteria after two cycles of treatment.. The purpose of the interim analysis is to determine whether it is futile to continue the study.

NUMBER OF SUBJECTS (PLANNED): 29

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Eligible patients must fulfil the following inclusion criteria:

1. Histologically or cytologically confirmed advanced not amenable to curative resection fibrolamellar carcinoma (FLC).
   a) This review will be conducted by a pathologist at the participating site to confirm the diagnosis. If there is a discrepancy, a review of a different archived specimen if available (heterogeneity is common) and/or identify a liver pathologist at another site who can provide independent review.
   b) Archived specimens will be collected for subsequent immunohistochemistry, genomic analysis and possibly other research.

2. All forms of prior local therapy are allowed as long as patients have either a target lesion, which has not been treated with local therapy and/or the target lesion(s) within the field of the local-regional therapy that has shown an increase of ≥ 20% in size. Local-regional therapy must be completed at least 4 weeks prior to the baseline CT scan.
3. Patients with prior systemic regimens are allowed. There is no limitation to the number of previous systemic regimens but must have recovered from any toxicity attributable to prioir therapy.
4. Are at least 4 weeks from major surgery or systemic therapy and recovered.
5. At least one measureable lesion by RECIST 1.1.
6. Male or non-pregnant, non-breastfeeding female at least 18 years of age. Patients aged at 12~18 years may be recruited but only at the site principle investigator's request and subject to IRB approval.
7. Have clinically acceptable laboratory screening results within certain limits specified below:
   - ∞ AST and ALT ≤ 5 times upper limit of normal (ULN)
   - ∞ Total bilirubin ≤ 3.0 x ULN
   - ∞ Creatinine ≤ 1.5 x ULN or Cr Cl > 60 cc/min
   - ∞ Absolute neutrophil count ≥ 1500 cells/mm^3
   - ∞ Platelets ≥ 50,000/mm^3
8. Have an ECOG performance status of 0-2 for ≥ 16 years of age and a Lansky performance status of 70-100 for < 16 years of age.
9. Women and men of child producing potential must agree to use effective contraceptive methods prior to study entry, during study participation, and for at least 30 days after the last administration of study medication. A serum pregnancy test within 72 hours prior to the initiation of therapy will be required for women of childbearing potential.
10. Have the ability to understand the requirements of the study, provide written informed consent or assent, which includes authorization for release of protected health information, abide by the study restrictions, and agree to return for the required assessments.

Eligible patients must not have any of the following exclusion criteria:

1. Have active, acute, or chronic clinically significant infections, chronic hepatitis or HIV, thromboembolic or hemorrhagic event with concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or Factor Xa inhibitors, or antiplatelet agents (eg, clopidogrel). Low dose aspirin (≤ 81 mg/day), low-dose warfarin (≤ 1 mg/day), and prophylactic low molecular weight heparin (LMWH) are permitted.

2. Have uncontrolled hypertension (systolic blood pressure greater than 150 or diastolic blood pressure greater than 100) or history of congestive heart failure (AHA Grade 2 or higher).
3. Have active cardiovascular disease.
4. QTc interval corrected for heart rate of greater than 470 msec in adults and 450 msec in pediatrics (< 18 years).
5. Have additional uncontrolled serious medical or psychiatric illness that in the point of view of the investigator can render the patient unable to receive therapy or make it unsafe to receive therapy.
6. Require treatment with any of the exclusionary medications listed in Appendix D.
7. Known untreated or unstable CNS metastatic disease.
8. Have persistent 2+ protein by urinalysis (patients with 2+ proteinuria that have a spot protein:creatinine ratio of less than 0.3 may be enrolled) or a history of nephrotic syndrome.
9. Subjects with history of another primary cancer, with the exception of: a) curatively resected non-melanoma skin cancer; b) curatively treated cervical carcinoma in situ; or c) other primary solid tumor with no known active disease present in the opinion of the investigator will not affect patient outcome in the setting of current FLC diagnosis.

TEST PRODUCT(S), DOSE AND MODE OF ADMINISTRATION: ENMD-2076 is provided as hard gelatin capsules containing 50 mg of drug.

Patients will receive a daily oral dose (fasting) of ENMD-2076 of 150, 200 or 250 mg/day based on body surface area.

DURATION OF TREATMENT: Following the Screening and Baseline Period (Day -28 to 1) each treatment cycle will consist of a 4-week Treatment Period (Cycle 1 to Cycle 6+). Patients will be treated until disease progression, unacceptable toxicity or death.

DISCONTINUATION FROM TREATMENT:
The Investigator or the Sponsor may discontinue individual patients from the study at any time. Patients will be encouraged to complete the study; however, they may voluntarily withdraw at any time. The Investigator or designee will document the reason for discontinuation. Patients who went off therapy without evidence of disease progression will have CT scans every two months until disease progression or death.

A patient will be withdrawn from treatment for the following reasons:

- ∞ Significant adverse event
- ∞ Pregnancy
- ∞ Disease progression
- ∞ Consent withdrawn
- ∞ Noncompliance

PRIMARY EFFICACY ENDPOINT:
Overall response rate based on RECIST v 1.1 criteria will be used to evaluate response every two months after first study drug administration. Patients who go off therapy without evidence of disease progression will have CT scans every two months until progression.

SECONDARY EFFICACY ENDPOINTS:

- ∞ Progression-free survival rate at 6 months (PFS6).
- ∞ The median PFS or TTP as based on RECIST 1.1 and measured by time from first study drug administration

until progression or death.

- ∞ The median overall survival as measured by time from first study drug administration to death or study completion.
- ∞ Safety data will be collected from time of informed consent through study completion /withdrawal up to 30 days after the last dose of study medication by each subject.

SAFETY ENDPOINTS:

Safety will be evaluated by collecting information on adverse events and by routine assessments. All adverse events will be graded using the NCI CTCAE version 4.0 and recorded in the CRF. Specific safety assessments include the following:

- ∞ Treatment-emergent AEs graded according to NCI CTCAE v4. The frequency and severity of AEs will be evaluated following administration of oral ENMD-2076
- ∞ Change from Baseline in vital signs (blood pressure, heart rate, respiratory rate, and body temperature)
- ∞ Change from Baseline in clinical laboratory tests from values obtained prior to treatment
- ∞ Change from Baseline in electrocardiograms (ECGs)

Serious adverse events require expedited reporting to the medical monitor as described in the protocol.

STATISTICAL ANALYSIS:

We have designed this study using a Simon's Optimal two-stage design to allow for an early interim analysis to determine potential futility and an overall final analysis with criteria established to allow for sufficient power and type 1 error rate to provide results to support this Phase 2 trial. The null hypothesis that the true response rate is 2% will be tested against a one-sided alternative that the true response rate is 15%. In the first stage, 16 patients will have reached study endpoints of response s per RECIST 1.1 criteria after two cycles of treatment. If there are zero responses in these 16 patients, the study will be stopped. Otherwise, 13 additional patients will be accrued for a total of 29. The null hypothesis will be rejected if 2 or more responses are observed in 29 patients. This design yields a type I error rate of 9.4% and power of 90% when the true response rate is 15%. The probability of early termination due to drug inefficacy is 72%.

DOCUMENT APPROVAL

PRINCIPAL INVESTIGATOR:

I have read and reviewed this Protocol 2076-CL-006, and I agree to conduct this trial according to this Protocol, to comply with its requirements subject to ethical and safety considerations, and to conduct the trial in accordance with all applicable regulations, Good Clinical Practice (GCP), Title 21 of the Code of Federal Regulations (CFR) sections 50, 56 and 312 and International Conference on Harmonization Guidelines on Good Clinical Practice (ICH E6). I further agree to comply with all other applicable federal, state, and local laws and regulations in connection with my conduct of this trial, including, without limitation, all applicable medical information privacy rule requirements.

I understand that the Sponsor may decide to suspend or terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the Sponsor.

CASI Pharmaceuticals, Inc. approves this protocol.

SPONSOR REPRESENTATIVE

Signature

16 Sept 2015

Date

Print Name: Rong Chen, MD, PhD,

Chief Medical Officer

PRINCIPAL INVESTIGATOR

Signature

Date

Print Name: _____

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2. LIST OF ABBREVIATIONS

AE	Adverse event
CR	Complete Response
CRF	Case report form
CT	Computed tomography
CTM	Clinical trial material
FLC	Fibrolamellar carcinoma
GCP	Good Clinical Practice
HCC	Hepatocellular carcinoma
IRB	Institutional Review Board
MRI	Magnetic resonance imaging
MUGA	Multi-gated acquisition scan
OS	Overall Survival
PD	Progressive Disease
PFS6	Progression Free Survival at 6 months
PR	Partial Response
SAE	Serious adverse event
SD	Stable Disease
TTP	Time to Progression
ULN	Upper limit of normal

3. ETHICAL CONDUCT OF THE STUDY AND REGULATORY REQUIREMENTS

3.1 Institutional Review Board (IRB)

The study protocol and any amendments will be reviewed by an Institutional Review Board (IRB). The IRB will review the informed consent form, their updates (if any), and any written materials given to the subjects. A list of all IRBs and contact information will be included in the study report.

3.2 Ethical Conduct of the Study

The study will be conducted in accordance the ethical principles that have their origins in the Declaration of Helsinki and in compliance with the Protocol, U.S. 21 CFR Part 312, current International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements.

3.3 Subject Information and Consent

The investigator will obtain a freely given written consent from each subject after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the study that are relevant to the subject's decision to participate. The consent form must be signed and dated by the subject before he/she is exposed to any protocol-specific procedure.

The investigator will explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, without any consequences for their further care and without the need to justify.

The patient will receive a copy of the patient information and the signed informed consent.

The patient will be informed if information becomes available that may be relevant to his/her willingness to continue participation in the study.

Each subject will be informed that a monitor or a health authority inspector, in accordance with applicable regulatory requirements, may review the portions of their source records and source data related to the study. Data protection and confidentiality will be handled in compliance with local laws.

3.4 Approval of the Study Protocol and Amendments

Substantive changes in the protocol include changes that affect the safety of patients or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of patients treated, or the patient selection criteria. Such changes must be prepared as a protocol amendment by the Study Monitor and implemented only upon joint approval of the Sponsor, Investigator, and the Study Monitor. A protocol amendment must receive IRB approval prior to implementation. In parallel with the

IRB approval process, the protocol amendment will be submitted to the appropriate regulatory authority as an amendment to the regulatory submission under which the study is being conducted. If a protocol amendment requires changes in the informed consent document, the revised informed consent document prepared by the Investigator must be approved by the Sponsor, Study Monitor, and the IRB.

Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular patient and that are deemed crucial for the safety and well-being of that patient may be instituted for that patient only. The Investigator or other attending physician also will contact the Medical Monitor as soon as possible in the case of such a departure. These departures do not require pre-approval by the IRB; however, the IRB and Medical Monitor must be notified in writing as soon as possible after the departure has been made. In addition, the Investigator will document in the patient's CRF the reasons for the protocol deviation and the ensuing events.

3.5 Ongoing Information for Institutional Review Board

While the study is ongoing and at study completion/discontinuation, the Investigator must submit to the IRB the following information in accordance with US Federal regulatory requirements:

- Information on serious or unexpected AEs showing due diligence in providing this information as soon as possible
- Periodic reports on the progress of the study
- Final Study Summary upon study completion or premature closure of study

3.6 Premature Closure of the Study

The Sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time and for any reason. If such action is taken, CASI Pharmaceuticals will discuss this with the Investigators (including the reasons for taking such action) at that time. CASI Pharmaceuticals will promptly inform all Investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigators must inform the IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to CASI Pharmaceuticals. In addition, the site must conduct final disposition of all unused study medication in accordance with CASI Pharmaceuticals procedures for the study.

Financial compensation to Investigators and/or institutions will be in accordance with the agreement established between the investigator and CASI Pharmaceuticals or designee.

The Investigators will submit a Final Study Summary to the institutional review board upon study completion or premature closure of the study.

4. INTRODUCTION

4.1 Background

Fibrolamellar carcinoma (FLC) is a rare malignant neoplasm of the liver. It has distinct clinical, histological and prognostic features from conventional hepatocellular carcinoma (HCC). It generally occurs in young individuals and is typically not associated with such underlying liver diseases as hepatitis and cirrhosis or other risks commonly present in HCC. FLC represents 0.6% to 8.6% of all hepatocellular carcinomas, according to 1986 to 1999 SEER data and various international series (El Serag et al., 2004; Sooklim et al., 2003; Moreno-Luna et al., 2005).

FLC is often advanced when diagnosed due to lack of symptoms (Yen and Chang 2009). Surgical resections are the optimal treatment for localized tumors, FLC has a very high recurrence rate. In cases of postoperative recurrence, resection is not often possible. As the tumor is quite rare, there is no standard first line systemic treatment option available. The survival rate for FLC largely depends on whether (and to what degree) the cancer has metastasized, i.e. spread to the lymph nodes or other organs (Ang et al., 2006). Overall prognosis remains poor, because of its primary chemo resistance and early recurrence of metastasis. The absence of treatment options highlights the need for new compounds with activity in this patient population. Tumor growth relies on angiogenesis, the formation of new blood vessels from pre-existing vascular beds, in order to receive an adequate supply of oxygen and nutrients (Semela and Dufour, 2004). Inhibition of angiogenesis may represent a therapeutic option in the treatment of FLC.

Recent clinical genomic research published in Science (Honeyman et al., 2014) reported the identification of a recurrent DNAJB1-PRKACA chimeric transcript that is expressed in 100% of FLC tumor tissue examined but not in adjacent normal liver, suggesting that this genetic alteration contributes to tumor pathogenesis of FLC. The chimeric RNA is predicted to code for a protein that is the catalytic domain of protein kinase A, which results in Aurora A kinase being overly expressed in FLC patients. Aurora kinases A, an important regulator in the cell proliferation process and often over-expressed in human cancers, is therefore believed to be a promising therapeutic target for FLC.

VEGF is one of the main inducers of liver tumor angiogenesis. Increased levels of VEGF have been observed in HCC. Hepatoma cells are believed to possess a proliferation mechanism regulated by an autocrine mechanism, a paracrine mechanism, or both, which are mediated by FGF-1/FGFR or FGF-2/FGFR (or both). In addition, a gain of FGF-R2 (IIIb), -R2 (IIIc), and -R3 (IIIb) may be associated with malignant transformation of liver tumor and may eventually serve as useful diagnostic and prognostic indicators (Asada et al., 2003).

4.2 Rationale

ENMD-2076 is an orally active, small molecule, multi-targeted kinase inhibitor with a mechanism of action against angiogenesis, proliferation and the cell cycle. ENMD-2076 has

selective activity against the mitotic kinase Aurora A, as well as kinases involved in angiogenesis (VEGFRs, fibroblast growth factor receptors-FGFRs) and cell growth (Src).

In pre-clinical *in vivo* animal model studies, ENMD-2076 exhibited anti-angiogenic activity by preventing the formation of new blood vessels and inducing regression of formed vessels at well-tolerated doses. ENMD-2076 induced strong tumor regression when administered orally in animal models of human tumors derived from leukemia, colon, and breast cancer cell lines with minimal toxicity.

In a pre-clinical study using three different human HCC cell lines, (SMMC-7721, QGY-7703 and HepG 2) were used to establish the tumor xenograft models in nude mice. After the inoculated tumors grew to more than 100 mm^3, mice were randomly assigned into one of the groups receiving vehicle, sorafenib, ENMD-2076 alone or in combination with chemotherapy agents, including doxorubicin or 5-FU, respectively, for 20 days. After commencing administration, dynamic measurement was performed every 3 days to determine the tumor sizes and body weights of the tumor-bearing mouse to assess tumor growth inhibition and adverse effects. In the SMMC-7721, QGY-7703 and HepG 2 xenograft models, ENMD-2076 induced tumor growth inhibition significantly greater ($P<0.01$ in all three models) than that of sorafenib. The tumor growth inhibition rates in the ENMD-2076 treated groups were also significantly higher ($P<0.01$ in all three models) than those seen in the groups treated with doxorubicin and 5 FU. These results show that ENMD-2076 demonstrated robust antitumor activity against three cell line-derived xenograft models of HCC, which is superior to that of sorafenib, doxorubicin, and 5FU, supporting clinical investigation of this agent in HCC patients who do not tolerate, or have failed or relapsed from other systemic treatment such as sorafenib, doxorubicin or 5 FU.
In clinical studies, clinical benefit has been observed with partial responses in one FLC patient, who relapsed from multiple treatments including TACE/doxorubicin, TACE/cisplatin, liver transplantation, and sorafenib. The patient was on ENMD-2076 for 18 4-week cycles while maintaining stable disease for 17 months.

There are, however, no first line systemic options available and few clinical trials currently under going to explore treatment of anti-angiogenic agents in FLC (NCT01642186).

The absence of current first line treatment options and the current anti-angiogenic clinical trial landscape make ENMD-2076 a viable candidate to potentially fill a currently unmet medical need in the treatment of FLC.

In order to address the urgency of the needs, FDA encourage studies of drugs or biological products for diseases that are life-threatening or severely debilitating in pediatric patients and that lack adequate therapy could begin earlier than studies of other products, despite the relative lack of safety and effectiveness information. (*FDA Guidance for Industry: How to Comply with the Pediatric Research Equity Act. September 2005*)

CASI Pharmaceuticals has submitted the study protocol to FDA and had a discussion about the study plan. FDA agreed the study dose regimen for the proposed age groups (12 years and above) with the current available pharmacokinetic and clinical data. FDA has granted orphan drug designation to ENMD-2076 for the FLC indication.

This protocol will evaluate efficacy and safety of ENMD-2076 in patients with FLC.

4.3 Potential Risks and Benefits

4.3.1 Risks of ENMD-2076

As of April 2014, 210 cancer patients have been enrolled in clinical studies of ENMD-2076. The most frequent treatment-related AEs in the clinical studies in advanced cancer patients include hypertension, fatigue, nausea, diarrhea, dizziness/light-headedness, mucositis, and pruritis/rash. Serious adverse events included fatigue, hypertension, gallbladder pain, cholecystitis, elevated liver function tests, hyponatremia, dehydration, mucositis, gastrointestinal bleed, neutropenia, dyspnea, exacerbation of congestive heart failure, speech impairment/aphasia, and acute asymptomatic pancreatitis. Other events reported in Phase 2 include decreased platelets, hand/foot syndrome, ischemic colitis, and thyroiditis.

Refer to the Investigator's Brochure for detailed safety information on the clinical and non-clinical studies.

4.3.2 Potential Benefits

It is unknown whether there will be an improvement of disease symptoms or survival in patients undergoing therapy with ENMD-2076. Patients who participate in this trial of ENMD-2076 will provide useful information that will guide its use in future patients with FLC.

5. STUDY OBJECTIVES

5.1 Primary Objective

The primary objective of this trial is to determine the overall response rate using RECIST v 1.1 criteria when patients with advanced fibrolamellar carcinoma (FLC) are treated with daily oral ENMD-2076.

5.2 Secondary Objectives

The secondary objectives are:

∞ To evaluate the 6-month progression free survival (PS6) rate using RECIST v 1.1 criteria when patients with FLC are treated with daily oral ENMD-2076.

∞ To evaluate the median Progression Free Survival (PFS), Time to Progression (TTP), and Overall Survival (OS).

∞ To determine the safety of ENMD-2076 as defined by the frequency and severity of adverse events when patients with FLC are treated with daily oral ENMD-2076.

∞ To explore biomarkers predictive of tumor response to ENMD-2076 in FLC patients

5.3 Endpoints

Revised RECIST criteria (version 1.1) as defined in Appendix C will be used to evaluate response. Response will be evaluated after every two cycles of treatment. Complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) will be defined as outlined in the revised RECIST criteria, Appendix C and Section 6.3. SD is defined if the disease is stable on two measurements or longer, i.e. 4 treatment cycles or longer. Progression free survival (PFS) is defined as the time from the first day of treatment to the first observation of disease progression or death due to any cause or last follow-up. PFS will be censored for patients who are alive and free of progression at the time of last follow-up. Duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). Patients who are removed from the study for reasons other than documented PD will be followed at 2 month intervals until study endpoint.

6. INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan – Description

This is a Phase 2 multi-center, open label study in 29 FLC patients. Patients will receive a daily oral dose (fasting) of ENMD-2076 as a single treatment agent. The starting dose will be based on body surface area. If adverse events, two dose reductions at the discretion of the investigator will be allowed for each patient. If adverse events resolve, the dose can be increased in 50 mg increments as tolerated. Dosing interruptions/delays will be allowed at the discretion of the investigator for recovery from adverse events or inter-current illness, particularly if the patient is benefiting from ENMD-2076 treatment. After a treatment interruption for adverse events, treatment can be resumed at a lower dose and increased in 50 mg increments as tolerated. Patients may be treated until disease progression or unacceptable toxicity.

Once a potential patient has been identified and signed the informed consent form, the screening and baseline visit procedures will be completed. Following the baseline visits, patients meeting all study entry criteria will start Cycle 1 and get their first dose of ENMD-2076. Each cycle of treatment consists of a 4-week treatment period. Patients who complete the initial cycle of therapy (4 weeks of treatment) without evidence of significant toxicity or clinical evidence of progressive disease may receive additional 4-week cycles of treatment.

Patients who discontinue therapy for any reason other than progression will continue to receive imaging until progression or death. All recruited subjects will be followed for safety and overall survival.

6.2 Discussion of Study Design and Choice of Control Group(s)

The primary objective of this trial is to determine the overall response rate using RECIST v 1.1 criteria when patients with advanced fibrolamellar carcinoma (FLC) are treated with daily oral ENMD-2076. Since there is no standard therapy approved to treat patients with FLC, it is appropriate for this evaluation to be conducted as a single arm, open label, non-controlled study.

The interim analysis with the initial 16 patients is to establish proof of concept before expanding the treatment to the full planned population of patients.

6.3 Selection of Study Population

6.3.1 Inclusion Criteria

The subjects must meet the following inclusion criteria:

1. Histologically or cytologically confirmed advanced not amenable to curative resection fibrolamellar carcinoma.

    a) This review will be conducted by a pathologist at the participating site to confirm the diagnosis. If there is a discrepancy, a review of a different archived specimen if available (heterogeneity is common) and/or identify a liver pathologist at another site who can provide independent review.

    b) Archived specimens will be collected for subsequent immunohistochemistry, genomic analysis, and possibly other research.

2. All forms of prior local therapy are allowed as long as patients have either a target lesion which has not been treated with local therapy and/or the target lesion(s) within the field of the local-regional therapy that has shown an increase of ≥ 20% in size. Local-regional therapy must be completed at least 4 weeks prior to the baseline CT scan.

3. Patients with prior systemic regimens are allowed,. There is no limitation to the number of previous systemic regimens but must have recovered from any toxicity attributable to prioir therapy.

4. Are at least 4 weeks from major surgery or systemic therapy and recovered.

5. At least one measureable lesion by RECIST 1.1.

6. Male or non-pregnant, non-breastfeeding female at least 18 years of age. Patients aged at 12~18 years may be recruited but only at the site principle investigator's request and subject to IRB approval。

7. Have clinically acceptable laboratory screening results within certain limits specified below:

    ∞ AST and ALT ≤ 5 times upper limit of normal (ULN)

- Total bilirubin ≤ 3.0 x ULN
- Creatinine ≤ 1.5 x ULN or Cr Cl > 60 cc/min
- Absolute neutrophil count ≥ 1500 cells/mm^3
- Platelets ≥ 50,000/mm^3

8. Have an ECOG performance status of 0-2 for ≥ 16 years of age and a Lansky performance status of 70-100 for < 16 years of age.

9. Women and men of child producing potential must agree to use effective contraceptive methods prior to study entry, during study participation, and for at least 30 days after the last administration of study medication. A serum pregnancy test within 72 hours prior to the initiation of therapy will be required for women of childbearing potential.

10. Have the ability to understand the requirements of the study, provide written informed consent or assent which includes authorization for release of protected health information, abide by the study restrictions, and agree to return for the required assessments.

6.3.2 Exclusion Criteria

The presence of any of the following excludes a subject from study enrolment:

1. Have active, acute, or chronic clinically significant infections, chronic hepatitis or HIV, thromboembolic or hemorrhagic event with concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or Factor Xa inhibitors, or antiplatelet agents (eg, clopidogrel). Low dose aspirin (≤ 81 mg/day), low-dose warfarin (≤ 1 mg/day), and prophylactic low molecular weight heparin (LMWH) are permitted.

2. Have uncontrolled hypertension (systolic blood pressure greater than 150 or diastolic blood pressure greater than 100) or history of congestive heart failure (AHA Grade 2 or higher).

3. Have active cardiovascular disease.

4. QTc interval corrected for heart rate of greater than 470 msec in adults and 450 msec in pediatrics (<18 years).

5. Have additional uncontrolled serious medical or psychiatric illness that in the point of view of the investigator can render the patient unable to receive therapy or make it unsafe to receive therapy.

6. Require treatment with any of the exclusionary medications listed in Appendix D.

7. Known untreated or unstable CNS metastatic disease.

8. Have persistent 2+ protein by urinalysis (patients with 2+ proteinuria that have a spot protein:creatinine ratio of less than 0.3 may be enrolled) or a history of nephrotic syndrome.

9. Subjects with history of another primary cancer, with the exception of: a) curatively resected non-melanoma skin cancer; b) curatively treated cervical carcinoma in situ; or c) other primary solid tumor with no known active disease present in the opinion of the investigator will not affect patient outcome in the setting of current FLC diagnosis.

6.3.3 Removal of Subjects from Therapy or Assessment

The Investigator or the Sponsor may discontinue individual patients from the study at any time. Patients will be encouraged to complete the study; however, they may voluntarily withdraw at any time. The Investigator or designee will document the reason for discontinuation. Patients who went off therapy without evidence of disease progression will have CT scans every two months until disease progression or death.

A patient will be withdrawn from treatment for the following reasons:

∞ Significant adverse event:

If a patient suffers an AE that, in the judgment of the Investigator, the Sponsor, or the Medical Monitor, presents an unacceptable consequence or risk to the patient, whether or not the AE is considered related to study medication, the patient will be withdrawn from treatment.

∞ Pregnancy

If a female patient becomes pregnant at any time during the study, she will be discontinued from further participation and treatment. See Section 8.3.7 for further information on recording and follow-up of pregnancies.

∞ Disease progression:

Progression by RECIST v. 1.1 criteria, unless in the judgement of the investigator the patient has derived benefit from the treatment.

∞ Consent withdrawn:

The patient chooses to terminate participation in the study.

∞ Noncompliance

Failure to receive or refusal of study medication.

Failure to comply with protocol requirements. The patient has a serious deviation from the protocol that would compromise the integrity of the study data. All occurrences of noncompliance must be documented on the appropriate CRF pages.

6.3.4 Replacement Policy

Withdrawn patients will not be replaced.

7. STUDY PRODUCT

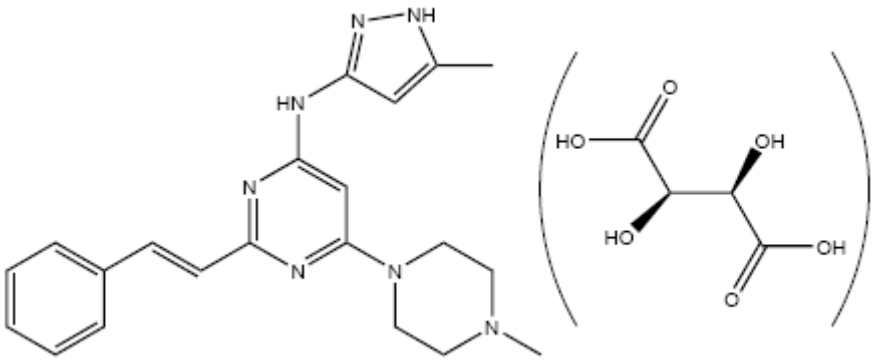
7.1 Study Medication Supply

CASI Pharmaceuticals will supply all ENMD-2076 clinical trial material (CTM), including study medication and supplies, to the study site. CTM will be shipped to the study site only after receipt of required documents in accordance with applicable regulatory requirements and standard operating procedures. The Principal Investigator, or authorized study personnel, upon receipt of the study medication supplies, will conduct an inventory and acknowledge receipt to CASI Pharmaceuticals, or designee.

7.2 Description of Study Product

ENMD-2076 is an off-white to yellow, odorless, crystalline solid manufactured by DSM Pharma Chemicals (DSM). The structural formula is illustrated in Figure 1.

Figure 1 Structural Formula of ENMD-2076



ENMD-2076 is provided as hard gelatin capsules and is intended for oral administration. The active pharmaceutical ingredient is chemically synthesized 2-(2-phenylvinyl)-4-[4-methylpiperazin-1-yl)]-6-(5-methyl-2H-pyrazol-3-yl-amino)-pyrimidine L(+) tartrate salt with an empirical formula of $C_{25}H_{31}O_6N_7 \cdot (2.5\ H_2O)$ and molecular weight of 570.59.

ENMD-2076 will also be supplied as 50 mg formulated pharmaceutical product filled into hard gelatin capsules, size 1 white body capsule. The composition of this formulated product is a granulated mixture comprised as noted in the Table 1 below. All components of the formulation are common excipients used in formulating a wide range of oral drug products.

Table 1: Composition of the Formulation for ENMD-2076 Capsules

Component	% in Final Mixture
Intragranular Component	
ENMD-2076	50%
MCC Avicel PH 101	30%

Methocel E5LV	3%
Sodium croscarmelose	3%
Cab-o-Sil (colloidal silicon dioxide)	0.5%
Mg Stearate (non-bovine #5712)	0.5%
Extragranular Component	
MCC Avicel PH 101	10%
Sodium croscarmelose	2%
Cab-o-Sil (colloidal silicon dioxide)	0.5%
Mg Stearate (non-bovine #5712)	0.5%
Total	100%

7.3 Description of Comparator Product

Not applicable.

7.4 Dosing

The planned starting dose for this study is approximately 160 mg/(m^2) of body surface area and is dosed in 50 mg increments per the following chart.

Body Surface Area (m^2)	Daily Dose
< 1.00	150 mg
1.00 - < 1.40	200 mg
≥ 1.40	250 mg

The Investigator will provide specific instructions to the patient regarding self-administration of each dose. All patients will be instructed to refrain from eating for one hour before and one hour following all doses.

If adverse events occur from treatment, two dose reductions at the discretion of the investigator will be allowed for each patient. If adverse events resolve, the dose can be increased in 50 mg increments as tolerated. Dosing interruptions/delays will be allowed at the discretion of the investigator for recovery from adverse events or inter-current illness, particularly if the patient is benefiting from therapy with ENMD-2076. After a treatment interruption for adverse events, treatment can be resumed at a lower dose and increased in 50 mg increments as tolerated.

Dose Adjustment Guideline for ENMD2076-related Toxicity	**Recommended Action**
Persistent (i.e. lasting more than 2 weeks despite optimal medical intervention) **OR** **Grade 2** toxicity that is deemed intolerable **OR** **Grade ≥3** toxicity	∞ Hold dose until toxicity resolves to Grade ≤1 or baseline (maximum 14 days). ∞ If the patient is benefiting from treatment but toxicity does not resolve to Grade ≤1 or baseline within 14 days of discontinuation of study drug, then study drug treatment

	may be delayed for an additional week. If toxicity persists despite the additional week off drug, then study drug will be discontinued permanently. ∞ If the toxicity resolves to Grade ≤1 or baseline within 14-21 days, restart drug administration as shown below.
First Reduction	∞ Allow toxicity to resolve to Grade ≤1 or baseline, then restart dosing at dose level -1, 200 mg/day
Second Occurrence	∞ Hold dose until toxicity resolves to ≤ Grade 1 or baseline (maximum 14 days). ∞ If the patient is benefiting from treatment but toxicity does not resolve to ≤ Grade 1 or baseline within 14 days of discontinuation of study drug, then study drug treatment may be delayed for an additional week. If toxicity persists despite additional week off drug, then study drug will be discontinued permanently. ∞ If the toxicity resolves to ≤ Grade 1 or baseline within 14-21 days then restart dosing at a dose level -2 (150mg/day)
Third Occurrence	∞ Discontinue study medication. ∞ If patient is benefiting from therapy, discuss with PI.

Each cycle of treatment consists of a 4-week treatment period. Patients who complete the initial cycle of therapy (4 weeks of treatment) without evidence of significant toxicity or clinical evidence of progressive disease may receive additional 4-week cycles of treatment.

If any individual patient develops ≥ 2+ proteinuria on qualitative assessment of protein on urinalysis, then a spot urine protein:creatinine ratio will be obtained, and a 24-hour urine collection will be obtained for quantification. If the spot protein:creatinine ratio remains equal to or below 1, then patients may continue to receive study drug until the 24-hour urine collection is complete (no longer than one week is allowed). If 24-hour urine shows greater than 3.5 g protein/24 hours then study drug will be held until the a repeat study shows a 24-hour urine below 3.5g.

7.5 Packaging and Labelling

ENMD-2076 will be packaged and labelled by AAI Pharma Services (Wilmington, NC) and stored by Fisher Clinical Services (Allentown, PA). Each bottle of bulk study drug will contain a label with the following information:

- ENMD-2076 50 mg
- CASI Pharmaceuticals Lot Number (example): 4392-001
- Contents: Number of capsules (100 capsules)
- Instructions: Take orally as directed
- Store at Ambient Temperature (15-25°C)
- Caution: New Drug – Limited by Federal Law to Investigational Use
- Sponsor: CASI Pharmaceuticals, Inc., Rockville MD, USA

7.6 Conditions for Storage and Use

ENMD-2076 will be stored under secure (with limited access), humidity-, and temperature-controlled conditions for the duration of the study until the material is returned to CASI Pharmaceuticals or destroyed by authorization from CASI Pharmaceuticals. The Study Monitor will inspect the drug storage area and review the drug accountability procedures discussed with the Investigator and personnel authorized to handle and/or dispense study drug. ENMD-2076 bottles will be stored at ambient temperature (15-25ºC) in an area accessible only to authorized staff. Patients will be asked to store their one-month supply of drug at ambient temperature. Study drug inventory forms will be kept by the Investigator, or designee, and examined and reconciled by the Study Monitor throughout the study.

7.7 Method of Assigning Subjects to Treatment Groups

This is a non-randomized study with all eligible patients assigned to active treatment with ENMD-2076.

7.8 Dispensing and Accountability

Study medication should only be dispensed once a patient has (1) signed an informed consent form, (2) met all eligibility criteria for entry into the study, (3) completed all screening and continuing eligibility requirements, and (4) been assigned a patient identification number.

Only patients enrolled in the study may receive study medication. Only authorized study personnel (the Investigator and his/her designees) may administer study medication, in accordance with all applicable regulatory requirements.

The investigator is responsible for maintaining accountability for the receipt, dispensing, and return of all study medication.

7.9 Patient Compliance

Authorized site personnel will administer the Day 1 dose of ENMD-2076. A one-month (+7 days) supply of study drug will be dispensed to each patient following the Day 1 study visit of each cycle. Patients will be instructed to return all empty study medication containers, any partially used or unused study medication, and daily diary pages at each visit to ensure compliance and record study drug accountability. If a patient realizes they miss a dose within 4

hours of the scheduled time, the dose should be taken. Otherwise, they should delay until the next day and consider the dose missed. Doses should not be repeated for any vomited doses. Any missed or vomited doses should be noted in their dosing diary.

Information regarding study medication administration and compliance will be recorded in the CRF.

A patient may refuse to take study drug or withdraw consent from further participation in the study at any time. Study site personnel will establish patient compliance with the study procedures and dosing at each visit.

7.10 Prior and Concomitant Therapy

All prescription and non prescription concomitant medications should be recorded on the appropriate page of the electronic case report form (eCRF).

The in vitro studies implicate the involvement of cytochrome P450 enzymes CYP3A4 in the pathways involved in the metabolism of ENMD-2076. No formal drug-drug interaction studies have been completed with ENMD-2076 and drugs that are substrates, inhibitors, or inducers of cytochrome P450 CYP3A4. Patients who require agents on the provided list in Appendix D will be excluded from enrolling in the study. Patients who require such an agent during participation in the study may be allowed to continue if the following apply: they have stable or responding disease (as confirmed by the Investigator); no alternative treatment is available; and they have close clinical monitoring while they are enrolled in the clinical trial.

Grapefruit juice is also a well-known inhibitor of CYP3A4 and should not be consumed during participation in the trial.

Concomitant treatment, in therapeutic doses, with anticoagulants such as warfarin or warfarin-related agents, heparin, thrombin or Factor Xa inhibitors, or antiplatelet agents (eg, clopidogrel) are not allowed. Low dose aspirin (≤ 81 mg/day), low-dose warfarin (≤ 1 mg/day), and prophylactic low molecular weight heparin (LMWH) are permitted.

Radioembolization is not allowed but will allow palliative radiation.

Any other medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the Investigator.

No other investigational agents are permitted during the entire duration of treatment with study drug.

8. EFFICACY AND SAFETY ASSESSMENTS

8.1 Primary Efficacy Variable(s)

Overall response rate using RECIST v 1.1 criteria. Response will be measured every two months after first study drug administration. Patients who went off therapy without evidence of disease progression will have CT scans every two months until progression.

8.2 Secondary Efficacy Variables

- 6-month progression free survival (PSF6) rate
- The median PFS and TTP as based on RECIST 1.1 and measured by time from first study drug administration until progression or death.
- The median Overall survival as measured by time from first study drug administration to death or study completion.
- Safety data will be collected from time of informed consent through study completion /withdrawal up to 30 days after the last dose of study medication by each subject.

8.2.1 Objective Tumor Responses/Benefit Assessments

Tumor responses in patients will be determined by the RECIST guidelines (version 1.1) defined in Appendix C. In the absence of significant treatment-related toxicity or clinical evidence of progressive disease, patients will be allowed to continue on 4-week cycles of ENMD-2076. The frequency and timing of the assessment of tumor burden/clinical benefit are described in Table 4. Unscheduled benefit assessments may be conducted when clinically indicated during the study.

-

8.2.2 Guidelines for Evaluation of Measurable Disease and Response

Guidelines for evaluation of measurable disease and response are outlined in Section 4 of Appendix C.

The same modality of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Details regarding method of assessment (i.e., CT scan) are outlined in Section 3.2.2 of Appendix C.

8.3 Safety Variables

Safety will be evaluated by collecting information on adverse events and by routine assessments. All adverse events will be graded using the NCI CTCAE version 4.0 and recorded in the CRF.

Specific safety assessments include the following:

- Treatment emergent AEs graded according to NCI CTCAE v4. The frequency and severity of AEs will be evaluated following administration of oral ENMD-2076

- ∞ Change from Baseline in vital signs (blood pressure, heart rate, respiratory rate, and body temperature)
- ∞ Change from Baseline in clinical laboratory tests from baseline values obtained prior to treatment
- ∞ Change from Baseline in electrocardiograms (ECGs)

Serious adverse events require expedited reporting to the medical monitor as described in the protocol

8.3.1 Clinical Laboratory

Non-fasting blood and urine specimens for the measurement and evaluation of clinical chemistry, hematology/coagulation, urinalysis, and pregnancy hormones (female patients with childbearing potential) will be collected as described in Table 2. Approximately 20 mL of blood will be collected for the clinical laboratory assessments at the specified times. Serum pregnancy tests will be performed as described inTable 4. A positive pregnancy test prior to dosing will exclude the patient from enrolment in the study. See Section 8.3.7 for requirements regarding pregnancies during the study. Values for the following parameters will be obtained:

Table 2 Non-fasting blood and urine specimens (Measurements and evaluation of clinical chemistry, hematology/coagulation, urinalysis, and pregnancy hormones)

HEMATOLOGY	CLINICAL CHEMISTRY	URINALYSIS
Hemoglobin Hematocrit Platelet Count White Blood Cell Count Differential, including: Neutrophils Lymphocytes Basophils Monocytes Eosinophils	Total protein Albumin Creatinine Uric acid Bilirubin (conjugated and total) Alkaline phosphatase AST(SGOT) ALT (SGPT) Glucose Calcium Phosphorus Bicarbonate Chloride Sodium Potassium Magnesium	Color/appearance Specific gravity pH Protein (qualitative)* Glucose (qualitative) Ketones (qualitative) Bilirubin (qualitative) Blood (qualitative) Standard microscopic examination if above parameters are abnormal
COAGULATION TESTS		**OTHER**
Prothrombin time (PT) or International Normalized Ratio (INR) Partial thromboplastin time (PTT)		Serum Pregnancy Test (according to study schedule)

* If Grade 2, then 24-urine must be obtained.

The results of clinical laboratory tests conducted during the study must be assessed by the Investigator to determine each patient's continuing eligibility for participation in the study. If values are outside the normal reference range, the Investigator must determine clinical significance within the context of the study and the patient's baseline. Clinically significant abnormal laboratory parameters occurring during the study are reported as AEs.

8.3.2 Medical History and Physical Examination

As part of the physical examination, a medical history will be taken with particular attention to (1) a review of the body systems, including diagnosis of malignancy; and (2) use of prescription medications, including prior chemotherapy and corticosteroids, and nonprescription medications.

Physical examination findings within the following categories will be assessed:

- HEENT
- pulmonary
- cardiovascular
- GI/abdomen
- extremities
- neurological
- skin and hair
- weight

The Screening Visit will also include measurement of height.

8.3.3 Standard 12-lead Electrocardiograms (ECGs)

A standard 12 Lead ECG will be performed at the times described in Table 4. In the case of an abnormal ECG, the ECG should be repeated to rule out machine error or improper placement of leads and reviewed by a local cardiologist. Any abnormality determined to be clinically significant by the Investigator should be discussed with the Medical Monitor prior to enrolment of the patient.

Any ECGs deemed abnormal by the Investigator may be over read by a cardiologist to make a determination of clinical significance. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings.

8.3.4 Vital Signs

Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. These parameters will be measured as described in Table 4. Vital sign measurements will be conducted after several minutes in the sitting position.

8.3.5 ECOG Performance Status

The Investigator will assess each patient's functional status using the ECOG Performance Status Scale at the time points identified inTable 4. Eligible patients must have an ECOG Performance Status of 0 to 2 at screening (see Appendix B).

8.3.6 Adverse Events

8.3.6.1 Adverse Events (AE) and Serious Adverse Events (SAE)

An adverse event (AE) is any untoward medical occurrence in a subject participating in a clinical trial. An adverse event can be any unfavorable and unintended sign, symptom or disease

temporally associated with the use of the study medication, whether or not considered related to the study medication. AEs will be collected from the start of treatment until 30 days following the final visit dose. Any events occurring prior to treatment will be recorded on the medical history page with the event name and onset date and end date if not continuing. Pre-existing, known clinically significant conditions observed at screening should be recorded as medical history.

This definition also includes accidental injuries, reasons for any change in medication (drug and/or dose) other than planned titration, reasons for admission to a hospital, or reasons for surgical procedures (unless for minor elective surgery for a pre-existing condition). It also includes adverse events commonly observed and adverse events anticipated based on the pharmacological effect of the study medication. Any new laboratory abnormality assessed as clinically significant by the Investigator must be recorded as an adverse event.

A treatment emergent adverse event is any adverse event occurring after start of study medication and within the time of residual drug effect, or a pre-treatment adverse event or pre-existing medical condition that worsens in intensity after start of study medication and within the time of residual drug effect.

Adverse events should be recorded as diagnoses, if available. If not, separate sign(s) and symptom(s) are recorded. One diagnosis/symptom should be entered per record.

Note that death is not an event, but the cause of death is. An exception is the event of sudden death of unknown cause. Note that hospitalization is not an event; however, the reason for hospitalization is. Procedures are not events; the reasons for conducting the procedures are. In general, only the reason for conducting the procedure will be captured as an adverse event. However, if deemed necessary by the Investigator, a procedure can be captured along with the reason for conducting the procedure.

An overdose or medication error is not an adverse event unless it is temporally associated with an unfavourable or unintended sign or symptom.

Each AE is to be classified by the investigator as serious or non-serious. A serious adverse event (SAE) is any untoward medical occurrence or effect that occurs at any dose:

- ∞ Results in death
- ∞ Is life-threatening (i.e., an immediate risk of death)
- ∞ Requires in-patient hospitalization or prolongation of existing hospitalization
- ∞ Results in persistent or significant disability/incapacity
- ∞ Is associated with a congenital anomaly/birth defect
- ∞ Is an important medical event

An adverse event caused by an overdose or medication error is considered serious if a criterion listed in the definition above is fulfilled.

Important adverse events that may not result in death, may not be life-threatening, or do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject's safety or may require medical or surgical intervention to prevent one of the outcomes listed above.

Serious adverse events also include any other event that the investigator or sponsor judges to be serious or which is defined as serious by the regulatory agency.

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial subject using concise medical terminology. In addition, each trial subject will be questioned about adverse events. The question asked will be "Since you began taking the study medication, have you had any health problems?"

8.3.6.2 Clinical Laboratory Abnormalities and Other Abnormal Assessments

It is the responsibility of the Investigator to assess the clinical significance of all abnormal laboratory values. The Investigator will exercise medical judgment in deciding whether abnormal laboratory values are clinically significant and represent AEs. In some cases, significant changes within the range of normal will require similar judgment by the Investigator.

If an abnormal laboratory value or assessment is clearly related to a medically defined diagnosis or syndrome, the diagnosis or syndrome will be recorded on the AE page, not the individual laboratory values. Clinically significant abnormal laboratory values should not be listed on the AE page of the eCRF, unless clinical signs or symptoms are present.

All clinically significant abnormal laboratory results or assessments will be followed until they return to normal or become stabilized (up to 30 days after end of study drug administration).

8.3.6.3 Procedures for Assessing, Recording, and Reporting Adverse Events and Serious Adverse Events

Throughout the duration of the study, the Investigator will closely monitor each subject for evidence of drug intolerance and for the development of clinical or laboratory evidence of adverse events. All adverse events (expected or unexpected) which occur during the course of the study, whether observed by the Investigator or by the subject, and whether or not thought to be drug-related, will be reported and followed until resolution or until they become stable.
The Investigator will evaluate AEs according to the following guidelines:

- **NCI CTCAE Version 4.0.** The Investigator must assign a CTC Grade for each AE (Appendix A)
- **Description of event** (if the event consists of a cluster of signs and symptoms, a diagnosis must be recorded [*e.g.*, flu syndrome] rather than each sign and symptom)

- **Onset Date**
- **Stop Date**
- **Seriousness** (see definition of SAEs, Section 8.3.6.1)

  The Investigator must record whether or not the AE meets the definition of serious. If the event is serious, the Investigator must complete a Serious Adverse Event report form (see Section 8.3.6.4). CASI Pharmaceuticals or designee will monitor the completeness and accuracy of these forms.

- **Relationship to Study Medication**

  The Investigator must assess the relationship between the AE and the study medication as either not related or having a possible, probable, or definite relationship to the study medication.

- **Outcome**

  Outcome of AEs should be recorded based on the status of the AE at discontinuation from the study (includes 30 days post last dose) as resolved, resolved with sequelae, ongoing or death. If an AE is not resolved at the time of discontinuation, the AE should be followed until resolution (return to normal or baseline values) or until judged by the Investigator to be no longer clinically significant.

- **Action Taken** (None, AE Required Treatment, Temporarily Interrupted or Permanent Discontinuation of Study Medication)
- **Patient Status** (*i.e.,* Was patient prematurely discontinued due to AE?)

Events will be coded into one of the following causality categories as defined below:

Category	Definition
Unrelated	Clearly and incontrovertibly due only to extraneous causes, and does not meet criteria listed under possible or probable.
Unlikely	Does not follow a reasonable temporal sequence from administration. May have been produced by the subject's clinical state or by environmental factors or other therapies administered.
Possible	Follows a reasonable temporal sequence from administration, but may have been also produced by the subject's clinical state, environmental factors or other therapies administered.
Probable	Clear-cut temporal association with administration with improvement on cessation of investigational medicinal product or reduction in dose. Reappears upon rechallenge. Follows a known pattern of response to the investigational medicinal product.

Adverse events with the causality assessed as unrelated or unlikely are categorized as not related to study medication.

Adverse events with the causality assessed as possible or probable are categorized as related to study medication and are called adverse drug reactions.

8.3.6.4 Reporting of Serious Adverse Events

An AE that is serious or potentially serious requires the following additional detailed reports and follow-up and should be recorded in the CRF. The content of these detailed reports should address the Investigator's (or in some cases, the Sponsor's) estimate of causality, and whether or not the AE is identified in nature, severity, and frequency in the Investigator's Brochure or in other risk information that has been supplied to the Investigator.

Sponsor Notification

Any SAE that occurs after starting study drug administration must be reported to the Clinical Study Monitor or Project Manager as soon as information is available. In turn, the Clinical Study Monitor/Project Manager must immediately inform the Medical Monitor of the event and document the notification in a telephone/contact report. The urgency for reporting a SAE is three-fold: (1) to facilitate discussion (and implementation, if necessary) by the Sponsor and the Investigator of appropriate follow-up measures; (2) to facilitate Investigator reporting of unanticipated problems involving risk to human patients to the IRB/REB; and (3) to enable the Sponsor to fulfil the requirements to the appropriate regulatory authority.

Any non-fatal or non-life-threatening SAE, regardless of expectedness or causality, or fatal or life-threatening SAE must be immediately reported to the Clinical Study Monitor or Project Manager by telephone or facsimile, and a written report (Serious AE Report Form) signed by the Investigator must be provided to the Clinical Study Monitor or Project Manager promptly, but no later than the timelines outlined in Table . This documentation will be forwarded to the Medical Monitor immediately to facilitate the prompt detection by the Medical Monitor of any changes in the nature, severity, or frequency of serious AEs, and allow the Sponsor to meet reporting requirements of the appropriate regulatory agency.

Table 3 Serious Adverse Event Reporting Requirements for Protocol 2076-CL-006

<table>
<tr><th rowspan="2">Communication</th><th colspan="2">Initial Reports</th><th>Follow-Up Reports</th></tr>
<tr><th>Fatal or Life-Threatening SAE</th><th>Other SAEs</th><th>Any SAE</th></tr>
<tr><td>Vendor SAE Portal*/ Telephone/Fax/Email</td><td>Immediately**
Vendor SAE Portal*/ Telephone/Fax</td><td>Within 24 hours**
Vendor SAE Portal*/ Telephone/Fax/Email</td><td rowspan="2">Prompt notification required no later than 48 hours**
Update Vendor SAE Portal</td></tr>
<tr><td>Written</td><td>Within 48 hours**
Vendor SAE Portal</td><td>Within 48 hours**
Vendor SAE Portal</td></tr>
<tr><td colspan="4">*If the SAE Portal is not available, alternative modes of communication must be used to report within the</td></tr>
</table>

specified time frames.

**The time period for notification of an SAE begins when the Investigator or any site personnel obtains knowledge of the event.

Institutional Review Board Notification

The Investigator must also promptly notify the IRB/REB of the SAE, including any follow-up information in accordance with local institutional policy.

If a given SAE is associated with the study medication and is unexpected, CASI Pharmaceuticals will forward an Investigational New Drug application (IND) Safety Report to the regulatory authorities and to the Investigator(s). In accordance with FDA regulations, it is the Investigator's responsibility to promptly inform the IRB/REB of the IND Safety Report.

Significant or Unexpected Toxicities

CASI Pharmaceuticals, the Medical Monitor, and the involved Investigator will monitor the safety experience of all patients treated. Significant or unexpected toxicities that, in the judgment of the Investigator, the Sponsor, or the Medical Monitor, presents an unacceptable consequence or risk to the patient will result in discontinuation of the patient from further study participation. The Investigator will notify CASI Pharmaceuticals immediately of any significant or unexpected toxicities. The Investigator, CASI Pharmaceuticals, or the Medical Monitor will notify other investigators and all institutional review committees of important or unexpected toxicity. Treatment may be delayed to allow recovery from treatment-related toxicities and to consider if dose reductions are appropriate for continued therapy with ENMD-2076. A delay of up to 3 weeks is allowed for patients to return to baseline or Grade 1 from any treatment-related side effect. Treatment delays for events such as intercurrent illnesses will be discussed with the Investigator and Medical Monitor to determine if a patient may remain on study if a delay of more than two weeks is required.

Post Study Adverse Events

Investigators are not obligated to actively seek information on AEs or SAEs in former study participants who completed the end of study visit. However, the Investigator should promptly notify CASI Pharmaceuticals, or designee, if the Investigator learns of any SAE or death of a study patient within 30 days after a patient has discontinued study drug administration, and such event(s) is (are) reasonably related to the study medication.

Investigators should promptly notify CASI Pharmaceuticals, or designee, if they become aware of a former study participant who is one of the parents of a subsequently conceived child with a congenital anomaly (see below).

8.3.6.5 Follow-up of Adverse Events and Serious Adverse Events and Other Investigations

All SAEs must be followed until they are resolved (return to normal or baseline values), stabilized, or the patient is lost to follow-up and cannot be contacted. Supplemental measurements and/or evaluations may be necessary to fully investigate the nature and/or

causality of an AE or SAE. This may include additional laboratory tests, diagnostic procedures, or consultation with other healthcare professionals. If the patient dies during the study or within 30 days following the End of Study Drug Administration/Discontinuation, any postmortem findings (including histopathology) must be provided to CASI Pharmaceuticals, or designee. CRF data should be updated with any new information as appropriate.

8.3.7 Pregnancy Information

A serum pregnancy test will be performed on females to determine pregnancy status at the time points outlined inTable 4. If any female patient becomes pregnant while enrolled in the clinical trial, she will be withdrawn immediately. Any dispensed study medication must be returned to the clinical site. The Investigator must notify CASI Pharmaceuticals or designee by telephone within 24 hours of learning about the pregnancy. The Investigator must diligently follow the patient until delivery or termination of the pregnancy, providing necessary updated information to CASI Pharmaceuticals or designee. Generally, follow-up will occur within six to eight weeks following the estimated delivery date. Any premature termination of the pregnancy will also be reported.

Although pregnancy occurring in a clinical trial is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE and will be followed as such. A spontaneous abortion is always considered to be an SAE.

9. STUDY PROCEDURES AND FLOW CHART

A brief description of the chronological flow of the study is provided in the following sections.

A detailed time and event schedule is provided inTable 4. Time 0 is defined as the precise time of the first ENMD-2076 administration on Day 1. All other time points in this study are relative to these definitions.

Screening Period (Day -28 to Day 1):
Prior to the initiation of any protocol-specific screening assessments not generally performed as part of routine patient care; the patient must be given a complete explanation of the purpose and evaluations of the study. Subsequently, the patient must sign and receive a copy of an Informed Consent Form that was approved by the IRB. Once informed consent has been obtained, the eligibility of the patient will be determined, and Screening Period assessments will be performed.

Treatment Period (before dosing on Day 1 up to Day 28):
On Day 1 before the initiation of the treatment, patients will be evaluated and baseline values for the specific assessments will be obtained. Thereafter during the initial Treatment Period, patients will visit the clinic for evaluation of tolerability, safety, and efficacy. Evaluation visits will be scheduled as described inTable 4.

Table 4 Schedule of Assessments

Measurement/Treatment	*Screening*	*Baseline*	*Follow-up after study drug administration* [a]					
	Days –28 to 1	Day 1 (prior to dose)	Cycle 1			Cycle 2	Cycle 3 +	Subject Discontinuation [l]
			Day 1	Day 8	Day 15	Day 1 (day 29)	Day 1 (of Cycle 3+)	
Inclusion/Exclusion	X	X						
Informed Consent and HIPAA Authorization	X							
Medical/Cancer History	X							
Echocardiogram or MUGA	X					X[J]	X[J]	X[J]
Physical Examination [c]	X	X [b]				X	X[i]	X
Vital Signs (HR, temp, RR, BP)	X	X [b]		X	X	X	X[i]	X
12-lead ECG	X	X [b]	X [m]			X [m]	X [m,n]	X
ECOG Performance Status	X	X [b]				X	X	X
RECIST Assessment	X						X[k]	X
Histological [q] or cytological evidence for diagnosis	X							
Archived specimens for biomarker analyses and genomic testing [r]	X							
Tumor Biopsy [s] for subsequent biomarker analyses	X						X	X
Retained Plasma Sample with biopsy [t]	X						X	X
Hematology [c]	X	X [b]		X	X	X	X	X
Clinical Chemistry [c]	X	X [b]		X	X	X	X	X
Coagulation Tests [c]	X	X [b]					X [j]	
TSH level	X	X [b]				X		
Urinalysis [c,d]	X	X [b]				X		X
Pregnancy Test [e]	X	X [b]				X		
Dispense ENMD-2076			X			X	X[i]	
Tumor Marker AFP[f]		X				X	X[k]	X
Ammonia		X				X	X[k]	X

CT [g] (or MRI) of chest, abdomen, pelvis	X						X[g]	X
AE Monitoring		X	X	X	X	X	X[i]	X
Concomitant Medications	X	X	X	X	X	X	X[i]	X
Follow-up Phone calls								X[p]
Retained Plasma Sample Pharmacokinetics [o]			X	X	X	X	X	

AE = adverse event; BP = blood pressure; DCE-MRI = dynamic contrast enhanced magnetic resonance imaging; HIPAA = Health Insurance Portability and Accountability Act; HR = heart rate; RR = respiratory rate; TSH = thyroid stimulating hormone.

a. Each visit following Day 1 must be completed with ±3 days of the indicated visit day and each monthly visit must be completed within ±7 days of the indicated visit day.
b. Repeated only if more than 72 hours since screening assessments.
c. Specific tests are listed in the protocol.
d. If a patient develops 2^{+}proteinuria, then a 24-hour urine collection is required for quantification and a repeat urinalysis should occur every week until resolution.
e. Women of childbearing potential only.
f. Tumor markers need to be assessed within 3 days of Cycle 1 Day 1, on Cycle 2, Cycle 3, Cycle 5, etc, and at the end of treatment, but optional on even cycles after Cycle 2.
g. Baseline scans must be done within 28 days prior to entering study and performed two months after Cycle 1 Day 1 and every two months after (+/- 7 days window). CT Scan can be either liver tri-phasic or liver 4-phase but should be consistant throught the study.
h. AEs and concomitant medications are monitored continually while on study. (Patients are instructed to call with AE symptoms between scheduled visits).
i. Completed on Day 1 at each new cycle.
j. Completed if clinically indicated and by discretion by the Investigator.
k. Completed at Cycle 2 and every 2 cycles after baseline (ie. Day 1 of Cycle 3, Cycle 5, etc).
l. These procedures should be done if a patient reaches disease progression (which may occur at a scheduled visit) or if a patient withdraws for other reasons. For subjects that withdraw for other reasons a CT scan is required every two months until disease progression or death.
m. Electrocardiogram should be performed on Day 1 of each Cycle pre-dose and 4-6 hours post dose.
n. For Cycle 4 and beyond, Electrocardiogram may be omitted if all previous ECGs have been clinically insignificant by investigator discretion.

o. Blood samples for pharmacokinetic analysis will be drawn and processed in all patients prior to dosing on Day 1, Day 8 and Day 15 of Cycle 1, and Day 1 of Cycle 2 and Cycle 3, respectively.

p. After subject discontinues, a follow-up call should be done every three months for confirming survival.

q. This review will be conducted by a pathologist at the participating site to confirm the diagnosis. If there is a discrepancy, a review of a different archived specimen if available (heterogeneity is common) and/or identify a liver pathologist at another site who can provide independent review.

r. Tissue for biomarker study and genomic testing:
- For archived tissue, 10-12 slides or a tissue block should be provide;
- For tissue biopsy, multiple strips that is sufficient for biomarker study and genomic testing should be provided;
- The tissue should be shipped to Memorial Sloan Kettering Cancer Center for subsequent biomarker study.

s. Tumor Biopsy: Tumor biopsy (optional) baseline up to 30 days prior to initiation of dosing （if patient had a biopsy after any previous treatments, they would be exempt of this biopsy） and at the end of treatment Cycle 2 (or Day 1 of cycle 3) in line with the imaging for tumor measurement An additional optional biopsy at the time of disease progression will be performed in patients who have complete response, partial response or stable disease for > 16 weeks.

Tumor biopsy for minor patients will only occur if medically indicated and not solely for research purposes. If available, a sample of tumor tissue from any surgical resection or biopsy during treatment or at time of progression will be requested for biomarker and genomic testing on this study. The biopsy after cycle 2 and the optional biopsy at completion of therapy only refers to patients 18 years of age or older.

t. Retained Plasma Sample with biopsy: At the same time the biopsy is performed, i.e. at baseline and at the end of treatment Cycle 2 (or Day 1 of cycle 3).

9.1 Study Periods

9.1.1 Screening Period (Days –28 to –1)

Prior to performing any study procedures, the Investigator, or designee, will obtain written informed consent from the patient as described in Section 3.3. The patient's consent must be confirmed at the time of signature by the dated signature of the person conducting the informed consent discussions. A copy of the signed consent document must be given to the patient or the patient's legally authorized representative. "Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research. The Investigator will retain the original signed consent document.

The specific Screening assessments are described in Section 8. Results of all assessments/evaluations must be acceptable to the Investigator and to the Sponsor or their designee prior to treatment with study medication.

When all screening results are completed and eligibility is confirmed, the patient will be assigned a patient identification number.

9.1.2 Treatment Period

The assessments to be performed during the Treatment Period are described in Section 8 and the timing of the assessments is provided inTable 4. Assessments at each clinic visit following Day 1 must be completed within ±3 days of the indicated visit day for Cycle 1 and each monthly visit (Cycle 2+) must be completed within ±7 days of the indicated visit cycle (4-weeks).

9.1.3 End of Cycle 6 Assessment Time point

All patients will have radiographic assessments of their disease at 6 months/180 days unless CT scan has previously documented progression of their disease. For patients who are continuing to receive study drug at this time point, this radiographic assessment may be combined with their regular visit and list of assessments for the cycle.

9.1.4 End of Study Drug Administration Visit

End of study drug administration assessments will be completed for each patient as indicated inTable 4.

9.2 Study Procedures

9.2.1 Pharmacokinetic analysis

Blood samples will be drawn from all the patients enrolled prior to the dosing at Day 1, Day 8 and Day 15 (steady state) of Cycle 1, and day 1 of Cycle 2, and Cycle 3, respectively as outlined in Table 4.

4 mL blood will be collected in tubes containing heparin sodium. Following blood collection, samples will be cooled in an ice bath and centrifuged (at approximately 1500 rpm for 10 minutes) under refrigeration at a temperature of approximately 4°C within 30 minutes of collection. Plasma samples will be divided into2 aliquots of approximately equal volume and stored in suitably labelled tubes at -80±15°C (within 45 minutes of blood sample collection), pending assay. Samples will remain in an ice bath until placement in a freezer.
Plasma samples will be retained and plasma concentrations of ENMD-2076 and its major active metabolite ENMD-2060 will be analysed. The effects of gender, age, body weight and CLcr (creatinine clearance) on the steady state plasma concentrations will be evaluated to explore the drug's exposure-response relationships.
(A manual for the Pharmacokinetic analysis will be provided)

9.2.2 Tissue biomarker analysis:

Formalin-fixed paraffin embedded archival surgical tumor tissue samples obtained from patients will be used for immunohistochemical analysis of key markers of proliferation (phospho-histone H3 [pHH3], Ki67), tumour microvessels (CD31) and p53. Following paraffin removal and subsequent rehydration of sections 5 lm thick, antigen retrieval is performed by incubating slides for 10 min at 100 ^{o}C in 10 mM sodium citrate, pH 6.0 (p53, pHH3, Ki67) or 10 mM Tris, 1 mM ethylene diamine tetra-acetic acid (EDTA), pH9 (CD31). Slides are blocked in 10% donkey serum in phosphate buffered solution (PBS) for 1 h then incubated for 1 h with primary antibody diluted in 2% donkey serum-PBS. Antibodies and dilutions to be used are as follows: p53 mouse monoclonal clone DO-1 (1:2000), Santa Cruz; pHH3 (Ser10) mouse monoclonal (1:1000), Cell Signalling; Ki67 mouse monoclonal clone MIB-1 (1:200), Dako; CD31 mouse monoclonal clone JC70A (1:500), Dako.

Slides are incubated overnight with biotin conjugated donkey anti-mouse IgG (Jackson ImmunoResearch, 1:200), followed by incubation with horseradish peroxidase-conjugated streptavidin (Jackson, 1:200) for 1 h. After washing in PBS, slides are developed with 3,3' diaminobenzidine (Dako), followed by counterstaining with haematoxylin (Dako). All slides are digitally scanned using the ScanScope XT brightfield scanner (Aperio Technologies), with an Olympus 20 X/0.75NA objective lens (resolution ~0.5 microns/pixel). Images are visualized and analyzed using ImageScope (Aperio). Cells positive for pHH3 and Ki67 staining are counted using the accompanying Nuclear_v9 algorithm. The CD31 microvessel density (MVD) count is determined by locating three CD31- dense hotspots in each section and counting the number of CD31-positive loci in a high-power field area for each hotspot, then representing the average as number of microvessels (MV) per mm^2.

The tissue should be shipped to Memorial Sloan Kettering Cancer Center for subsequent biomarker studies and possibly other research..

9.2.3 Genomic testing

Paraffin embedded tumor tissue sections and one whole blood sample will be collected and processed for a 410 gene panel DNA sequencing analyses. The treatment and preservation of

tumor tissue will follow the routine operation procedures in pathology. Tissue blocks with high levels of tumor cells should be selected (weight 100~500 mg, diameter >5 mm). At least 15-20 unstained and charged slides should be provided, with a thickness of 10μm, along with one HE stained paraffin sections with a thickness of 5μm. Slides should be cut from the same source. The predicted tumor cells should be more than 50%. The tissue section samples will be shipped to MSKCC after collection for further testing and analysis. The tumor cell DNA will be extracted, sequenced and analyzed based on standard operational procedures at the MSKCC research laboratory. One whole blood sample should be collected in a 3mL EDTA lavender top tube and send to MSKCC. MSKCC's Center of Molecular Oncology will run its Integrated Mutation Profiling of Actionable Cancer Targets (IMPACT) battery of 410 cancer genes on all samples provided. This information will be collected for research purposes only.

9.2.4 Tumor biopsy:

Tumor biopsies will be performed as per local institutional guidelines. Tumor biopsy (optional) baseline up to 30 days prior to initiation of dosing （if patient had a biopsy after any previous treatments, they would be exempt of this biopsy） and at the end of treatment Cycle 2 (or Day 1 of cycle 3) in line with the imaging for tumor measurement An additional optional biopsy at the time of disease progression will be performed in patients who have complete response, partial response or stable disease for > 16 weeks. If either the baseline or post-treatment biopsy is unable to be obtained due to technical issues (after consenting the patient and making a reasonable effort), the patient is still eligible to participate in the study. A third optional biopsy will take place at the time of disease progression for patients who have complete response, partial response, or stable disease for ≥ 16 weeks. Biopsy samples obtained pre- or after treatment will also be used for biomarker analysis using immunohistochemistry methods as described above. For tissue biopsy, multiple strips that are sufficient for biomarker study should be provided.

A 3mL blood sample will be collected at each time the biopsy is performed. The blood will be drawn in an EDTA tube and MSKCC's Center of Molecular Oncology will run the sample on its Integrated Mutation Profiling of Actionable Cancer Targets (IMPACT) battery of 410 cancer genes. The sample may also be used to identify predictive biomarkers of response, sensitivity and clinical benefit to ENMD-2076.

Tumor biopsy for minor patients will only occur if medically indicated and not solely for research purposes. If available, a sample of tumor tissue from any surgical resection or biopsy during treatment or at time of progression will be requested for biomarker and genomic testing on this study. The biopsy after cycle 2 and the optional biopsy at completion of therapy only refers to patients 18 years of age or older.

(A manual for the Pathology tissue and Tumor biopsy will be provided)

10. STATISTICAL METHODS PLANNED AND SAMPLE SIZE

10.1 Subject Populations

All enrolled patients who receive at least one dose of study medication will constitute the safety population. The safety population will be used for all demographic and baseline characteristics analyses and for all safety analyses.

The per-protocol population will include all evaluable patients in the safety population who do not have a major protocol deviation. Efficacy assessments will be analyzed for the safety and per-protocol population. The analysis on the safety population should be considered primary.

10.2 Subject Disposition

This study is an open-label trial; patients will be allowed to continue study drug treatment until disease progression or toxicity occurs. Patients will remain on study for at least 6 months/180 days. No interim analysis or data safety monitoring beyond that described above will be conducted for this study.

10.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics of subjects will be summarized with descriptive statistics.

10.4 Efficacy Analysis

We have designed this study using a Simon's Optimal two-stage design to allow for an early interim analysis to determine potential futility and an overall final analysis with criteria established to allow for sufficient power and type 1 error rate to provide results to support a submission of the study as a pivotal trial.

For the primary endpoint, the overall response rate will be examined using the RECIST v 1.1 criteria. Patients will first be examined in one of 4 categories – CR, PR, SD, PD (Complete response, Partial Response, Stable Disease, or Progressive disease, respectively). Next, patients will be dichotomized as responders (CR/PR versus non-responders). The null hypothesis that the true response rate is 2% will be tested against a one-sided alternative that the true response rate is 15%. In the first stage, 16 patients will have reached study endpoints of response s per RECIST 1.1 criteria after two cycles of treatment. If there are zero responses in these 16 patients, the study will be stopped. Otherwise, 13 additional patients will be accrued for a total of 29. The null hypothesis will be rejected if 2 or more responses are observed in 29 patients. This design yields a type I error rate of 9.4% and power of 90% when the true response rate is 15%. The probability of early termination due to drug inefficacy is 72%.

After the primary efficacy analysis is performed, a one-sided 95% confidence interval will be calculated using the Clopper-Pearson exact method for the response rate. This will determine the

lower bound for the response rate. If 2 or more patients respond out of 29 then the lower bound will exceed 1.2% providing evidence that the drug is active (i.e. ruling out 0% response).
For each of the secondary endpoints, exploratory analyses will be performed. Progression Free Survival rate at 6 months (PFS6) and three time-to-event measures will be calculated. Time to Progression, progression free survival and overall survival. A Kaplan-Meier survival plot will be calculated for each of these measures and median time to event (i.e. survival) will be calculated for each measure.

10.5 Safety Analysis

Safety will be assessed by evaluation of adverse events and clinical laboratory results.

10.5.1 Adverse Events

Adverse events will be coded to system organ class and preferred term using MedDRA version 16.0 or higher. All adverse events occurring after the initiation of the study treatment (treatment emergent adverse events) will be reported, including events present at baseline that worsened during the study.

Adverse events will be summarized by treatment group to provide visual comparison among the treatment groups with respect to incidence of adverse events (the number of subjects reporting at least one episode of a specific adverse event), incidence of adverse events by severity within body system, incidence of adverse events by attribution within body system, and incidence of adverse events causing withdrawal and incidence of serious adverse events. Regarding severity and attribution summaries, the most extreme outcome (highest severity and closest to study drug related) will be used for those subjects who experience the same adverse event on more than one occasion.

Written narratives will be provided for all serious, unexpected or other significant adverse events that are judged to be of special interest because of their clinical importance.

10.5.2 Clinical Laboratory

Clinical laboratory results will be summarized with descriptive statistics at baseline each study timepoint and with shifts from baseline.

11. QUALITY CONTROL AND QUALITY ASSURANCE

10.6 Source Data and Records

Source data are all the information in original records and certified copies of original records of clinical findings, observations, laboratory reports, data sheets provided by the sponsor or other activities in the study, which are necessary for the reconstruction and evaluation of the study. The investigator will permit study-related monitoring, audit(s), IRB review(s) and regulatory inspection(s), with direct access to all the required source records.

All study records will be retained for a period of time as defined by the regulatory authority and per ICH E6 section 4.9 for the country in which the investigation is conducted. Generally, this means at least 2 years following the date on which the drug is approved by the regulatory authority for marketing for the purposes that were the subject of the investigation. In other situations (e.g., where the investigation is not in support of or as part of an application for a research or marketing permit), a period of 2 years following the date on which the entire clinical program is completed, terminated or discontinued or the investigational application under which the investigation is being conducted is terminated or withdrawn by the regulatory authorities.

In the event the Investigator retires, relocates or for any other reason withdraws from the responsibility for maintaining records for the period of time required, custody of the records may be transferred to any other person who will accept responsibility for the records. Notice of such a transfer must be given in writing to the Sponsor. The Investigator must contact the Sponsor prior to disposal of any records related to this study.

10.7 Reporting of Results

The Case Report Form (CRF) is an integral part of the study and subsequent reports. The CRF must be used to capture all study data recorded in the patient's medical record. The CRF must be kept current to reflect patient status during the course of the study. Only a patient screening and randomization number and patient initials will be used to identify the patient.

The monitor is responsible for performing on-site monitoring at regular intervals throughout the study to verify adherence to the protocol; verify adherence to local regulations on the conduct of clinical research; and ensure completeness, accuracy, and consistency of the data entered in the CRF.

CASI Pharmaceuticals, Inc. or a designated CRO will monitor completed Case Report Forms (CRFs). A case report form will be provided for each screened patient.

All protocol-required information collected during the study must be entered by the Investigator, or designated representative, in paper CRF or the Target e*CRF™, an Internet-based electronic data collection system, which is 21CFR Part 11 compliant.. All details of the CRF completion and correction will be explained to the investigator. The management module of Target e*CRF™ , if used, includes edit check and query systems that seamlessly integrate with the data

entry system. All modifications to the data in the eCRF are tracked by an electronic audit trail (date and identity of the person making the change are instantaneously recorded). The actual date (and time, if applicable) of each assessment should always be entered in the CRFs
If the Investigator authorizes other persons to make entries in the CRF, the names, positions, and signatures of these persons must be indicated on the Site Delegation Log.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. By design, an explanation must be provided for all missing data, altered data, and/or out of range data.

The completed case report form must be reviewed and signed by the Investigator named in the study protocol or by a designated sub investigator after all the data was monitored and verified as final by the designated study monitor.

Final monitored and audited CRFs will be provided by the Sponsor to the sites at the end of the study in the format of a PDF file.

10.8 Confidentiality of Subject Data

The investigator will ensure that the confidentiality of the subjects' data will be preserved. In the CRF or any other documents submitted to the sponsor, the subjects will not be identified by their names, but by an identification system, which consists of their initials and number in the study. The investigator will maintain documents not meant for submission to the sponsor, e.g., the confidential subject identification code and the signed informed consent forms, in strict confidence.

11. REPORTING AND PUBLICATION

11.1 Confidentiality of Study Data

Any information relating to the study product or the study, including any data and results from the study, will be the exclusive property of the sponsor. The investigator and any other persons involved in the study will protect the confidentiality of this proprietary information belonging to SPONSOR.

11.2 Publication Policy

SPONSOR agrees to make the report of the multicenter study results available to investigators for preparing a publication of the results in meeting abstract or medical journal form. SPONSOR will have 30 days to review any proposed publication of the data for accuracy and proprietary information. The Study Chair has the first right of refusal of both first and last authorship position on manuscripts and meeting presentations.

12. REFERENCES

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13. APPENDIX A

National Cancer Institute Common Terminology Criteria for Adverse Events v. 4.03

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

14. APPENDIX B

ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

15. APPENDIX C

New Response Evaluation Criteria in Solid Tumors: Revised RECIST guideline (version 1.1)

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New Response Evaluation Criteria in Solid Tumors: Revised RECIST guideline (version 1.1). Eur J Cancer, 45:228-247, 2009.

16. APPENDIX D

Appendix D. Selected Inhibitors and Inducers of CYP3A4

Inhibitors	Inducers
Protease inhibitors: ritonavir indinavir nelfinavir saquinavir	Anticonvulsants, mood stabilizers: phenytoin (anticonvulsant) carbamazepine oxcarbazepine
Macrolide antibiotics: erythromycin telithromycin clarithromycin	Barbiturates: Phenobarbital
Azole antifungals: fluconazole ketoconazole itraconazole	Non-nucleoside reverse transcriptase inhibitors: efavirenz nevirapine etravirine
Nefazodone (psychoactive and antidepressant)	Rifampicin & rifabutin (bactericidal)
Bergamottin (constituent of grapefruit juice)	Modafinil (stimulant)
Quercetin (nutritional supplement)	Hyperforin (constituent of St Johns Wort)
Aprepitant (antiemetic)	Cyproterone (antiandrogen, progestin)
Verapamil & diltiazem (calcium channel blocker)	Pioglitazone & troglitazone (antidiabetics)
Chloramphenicol (antibiotic)	