

JAKaL

A phase Ib study of Itacitinib, a JAK1 inhibitor, in advanced hepatocellular carcinoma

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This protocol describes the JAKaL study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator

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1. INTRODUCTION AND RATIONALE

1.1 Background

Primary liver cancer consists predominantly of Hepatocellular Carcinoma (HCC). HCC is the fifth most common cancer in men, seventh in women and the third most common cause of cancer mortality (*de Lope C R, Tremosini S, Forner A, Reig M, Bruix J; Journal of Hepatology*2012;S75–S87). In addition, it is also the leading cause of death in patients with cirrhosis in Europe and the US (*Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet* 2003;362(9399):1907-17). Many patients diagnosed with HCC will have advanced disease where only palliative care is available to them, contributing to a relatively low reported 5-year survival rate of approximately 10%.

Growing information regarding the molecular mechanisms that induce and maintain hepatocarcinogenesis is important as HCC is rarely found in a background of a healthy liver. Major risk factors that have been linked to the development of HCC include alcohol induced liver disease, chronic Hepatitis C and B virus (HCV and HBV) infections; with cancer risk increasing sharply in response to chronic injury at the cirrhosis stage. Additional epidemiological and pre-clinical studies have also investigated chronic inflammatory conditions at specific organ sites which provide evidence that inflammation promotes malignant transformation.

The production of tumour-promoting cytokines by immune/inflammatory cells can activate transcription factors, such as STAT3 via the JAK/STAT pathway in premalignant cells. Once activated STAT3 drives the expression of multiple genes important for cell activation, localization, survival, and proliferation (Valentino and Pierre 2006). It is therefore hypothesised that the inhibition of JAK may directly affect malignant cell proliferation as well as possibly suppressing some negative effects related to the inflammatory state.

HCC patients have only limited non-surgical treatment options in the UK, with sorafenib and lenvatinib being the only licensed systemic treatments that provide a limited survival benefit. Therefore alternative novel approaches for the treatment of advanced HCC represents a high unmet medical need.

1.2 Itacitinib

Itacitinib is a small molecule inhibitor with selectivity for Janus Kinase 1 (JAK1) that is proposed for development for the treatment of myelofibrosis (MF), rheumatoid arthritis (RA), psoriasis, graft-versus- host-disease (GVHD), solid tumours, and B-cell malignancies. Members of the JAK family (JAK1, JAK2, JAK3, and TYK2) play an important role in signal transduction transmitting extracellular ligand binding into an intracellular response following the binding of cytokine and growth factor to their receptors.

JAKs are activated through a process of autophosphorylation enabling them to phosphorylate specific tyrosine residues on the cytokine receptors that serve as docking sites for multiple proteins, including latent STATs. The receptor-associated STATs (and other substrates) can then be phosphorylated by JAKs, resulting in their activation. Once activated STATs become transcription factors and drive the expression of multiple genes important for cell activation, localization, survival, and proliferation (Valentino and Pierre 2006).

1.2.1 Inhibition of JAKS as a target for Solid Tumours

In contrast to normal cells STATs (particularly STAT3) are persistently phosphorylated in most malignancies (Sansone and Bromberg 2012). The persistent or constitutive phosphorylation of STAT3 in cancers may occur via a variety of mechanisms, including increased expression of cytokines and cytokine receptors, decreased expression of the negative regulatory proteins such as suppressor of cytokine signalling (SOCS) through promoter methylation, and loss of tyrosine phosphatases that dephosphorylate JAKs and STATs.

Neoplastic progression involves JAK/STAT pathway activity through cell autonomous and non-cell autonomous mechanisms. Cell autonomous mechanisms refer to intrinsic alterations to the tumour cell that allow them to develop abnormal properties. The presence of STAT3 allows the cell the ability to sustain cell proliferation and block apoptosis (Lesina et al 2011); mediate cell cycle progression during oncogenic stress (Toyonaga et al 2003, Thoennissen et al 2009); control invasiveness, metastasis, and angiogenesis; and confer chemotherapeutic resistance (Catlett-Falcone et al 1999) as major mechanisms contributing to cancer. Non-cell autonomous mechanisms refer to the extrinsic effects mediated by tumour microenvironment, stroma, immune system, and stellate cells (Masamune et al 2005); these have been shown to play an integral role in pancreatic neoplasia and are substantially shaped to a great extent by JAK/STAT signalling.

In addition, JAK/STAT-dependent inflammatory cytokines such as IL-6 and IFN- γ are critical mediators of cancer cachexia, a significant cause for cancer morbidity and mortality. Based on this evidence, it is hypothesized that inhibition of JAKs may directly affect malignant cell proliferation and may suppress the inflammatory state leading to improvements in nutritional status, fatigue, tolerance to therapy, and prolonged survival in patients with advanced cancers that are driven by these intrinsic and extrinsic pathways influenced by STATs. This hypothesis is supported by evidence that JAK/STAT inhibitors are able to slow tumour cell growth and prolong survival in *in vivo* models (Thoennissen et al 2009, Toyonaga et al 2003, Iwanski et al 2010).

Further details can be found in the investigator brochure.

1.2.2 Pre-Clinical Studies

1.2.2.1 In Vitro Studies

The selective inhibition of JAK1 compared to JAK2 by Itacitinib has been demonstrated in biochemical assays; with additional analyses performed using cell-based assays known to signal through JAK2 homodimer (Murray 2007).

Effects of pathogenesis of RA, such as IL-2 stimulated phosphorylation of JAKs and STATs and IL-2- induced proliferation of cells; as well as the inhibition of phosphorylation of STAT proteins and the production of proinflammatory factors (eg, IL-17, MCP-1) induced by other cytokines, such as IL-23 and IL-6 have also been seen with ICNB039110.

Analysis of human INA-6 multiple myeloma cell line determined the ability of Itacitinib to inhibit cell growth by the inactivation of JAK/STAT3 through the withdrawal of IL-6 or inhibition of IL-6 binding to the IL-6 receptor which induces cell death via apoptosis (Burger et al 2001).

Whole blood assays were used to estimate the effectiveness of blocking JAK in hematopoietic cells *in vivo*, results showed Itacitinib blocked IL-6- induced STAT3 phosphorylation in human whole blood, whereas the potency of Itacitinib in blocking TPO-induced pSTAT3 was significantly reduced, consistent with the JAK1 selectivity measured in the biochemical assays.

Further details can be found in the investigator brochure.

1.2.2.2 Pre-Clinical Toxicology

The toxicology profile of Itacitinib was characterized in single- and multiple-dose oral studies, of up to 6 months in duration in rats and 9 months dogs, and in genetic, photo toxicity, and embryo-fetal developmental toxicology studies.

Single oral doses of Itacitinib up to 2000 mg/kg in rats produced no adverse effects. In multiple-dose studies in rats, dose-related body weight decreases and lower food consumption were noted. Pharmacology-related clinical pathology and anatomical alterations in multiple-dose rat studies included a reversible lowering of white blood cell (WBC) count, primarily because of a lower circulating lymphocyte count, a reversible lymphoid depletion in lymphoid tissues, and a reduction in bone marrow cellularity. The NOAEL in the 6-month rat study was determined to be 300 mg/kg per day for both males and females.

Single oral doses of Itacitinib of up to 1000 mg/kg in dogs produced no adverse effects. In multiple-dose studies in dogs, gastrointestinal (GI) inflammation was determined to be the dose-limiting toxicity (DLT) in studies of up to 3 months in duration. In the 6- and 9-month studies, generalized demodicosis, an effect secondary to the immunosuppressive effect of Itacitinib, was the DLT. The NOAEL in the 9-month study was determined to be 10 mg/kg per day.

Itacitinib was not genotoxic in the bacterial mutagenicity assay, the *in vitro* chromosome aberration assay in human lymphocytes, or the *in vivo* micronucleus assay in rats. Itacitinib did not demonstrate phototoxic potential in the *in vitro* neutral red uptake photo toxicity study.

When administered to pregnant rats and rabbits, Itacitinib caused fetotoxicity and fetal malformations and variations only at the highest doses tested. In the rat, all fetal effects were considered secondary to Itacitinib administration because of severe maternal toxicity observed at the same dose level as the fetotoxicity.

Further details can be found in the investigator brochure.

1.2.3 Clinical Studies

As of the data cutoff date (30 APR 2021), 34 clinical studies with itacitinib (18 Phase 1, 7 Phase 1/2, 7 Phase 2, and 2 Phase 3), including studies of itacitinib as monotherapy and in combination with chemotherapeutic agents, corticosteroids, CNI-based interventions, pembrolizumab (anti-PD-1 monoclonal antibody), tyrosine kinase inhibitors (ibrutinib and osimertinib, investigational PI3Kδ (INCB040093 and pascalisib), a JAK inhibitor (ruxolitinib), and an IDO1 (epacadostat) inhibitor, have either been completed or are ongoing.. In addition, a rollover study has been initiated for participants who were continuing to receive benefit from treatment with itacitinib at the time of their study's closure. As of the cutoff date, approximately 1699 unique participants, which includes 543 healthy adult participants, have been exposed to itacitinib..Phase 1 included 11 completed studies.

- **INCB 39110-101** was a Phase 1, double-blind, randomized, placebo-controlled, single-dose escalation study to assess the safety, tolerability, and PK of Itacitinib when administered orally to healthy adult subjects. This study was conducted in 3 cohorts of up to 12 subjects each. Cohort 1 received single doses of 10 mg, 50 mg, 200 mg, and 500 mg with at least 2 weeks between doses. Cohort 2 received single doses of 20 mg, 100 mg, and 300 mg with at least 2 weeks between doses. Cohort 3 received a single dose of 1000 mg.
- **INCB 39110-102** was a Phase 1, relative bioavailability study of 4 Itacitinib SR formulations compared with the IR formulation, and evaluated the effect of food on the SR formulations in healthy adult subjects. This study employed a 3-period crossover design with subjects randomized to various sequences of SR

fasted, SR fed (after a standardized high-fat meal), and IR fasted with 1 week between doses. Five cohorts of 12 subjects were evaluated with single 300 mg doses of IR, SR1, SR2, SR3, and SR4 formulations. Also, 6 subjects in Cohort 1 were evaluated with a microdose of ¹⁴C-Itacitinib (700 nCi/0.008 mg) in 50 mg liquid with 250 mg in tablets in a fourth study period. Cohort 6 evaluated doses of 50 mg Itacitinib SR3 (administered as two 25 mg tablets) and 100 mg SR3 (one 100 mg tablet) in the fed and/or fasted states in 12 additional healthy adult subjects.

- **INCB 39110-103** was a Phase 1, double-blind, randomized, placebo-controlled, multiple-dose escalation study to assess safety, tolerability, and PK of Itacitinib when administered orally to healthy adult subjects. Five cohorts of up to 12 subjects completed dose administration of Itacitinib SR1 200 mg BID, 400 mg BID, and 600 mg BID in the fasted state and 400 mg and 600 mg BID in the fed state (medium-fat meal). Two cohorts of up to 12 subjects completed dose administration of doses of Itacitinib SR3 400 mg BID and 800 mg QD in the fed state (medium-fat meal).
- **INCB 39110-105** Open-label, randomized, crossover, Phase 1 study, to assess Relative bioavailability of IR and SR tablets and food effect. Itacitinib 200, 300, or 600 mg SR or IR PO after fast of ≥ 10 hours, after a high-fat meal, or after a medium-fat meal. 129 healthy adult participants
- **INCB 39110-109** Open-label single-centre Phase 1 study to assess PK-mass balance and metabolite profile, Itacitinib 300 mg SR PO + 100 mL [¹⁴C] Itacitinib adipate 500 μ Ci (~4.9 mg). 7 Healthy participants aged 18 to 55 years
- **INCB 39110-111** Open label, phase 1 trial of 42 healthy participants 18-55 yrs old to Compare relative bioavailability of Itacitinib 200 mg SR tablets (test) with Itacitinib 2 \times 100 mg SR tablets
- **INCB 39110-115** was a Phase 1, double-blind, randomized, placebo-controlled, multiple-dose study to assess the effect of Itacitinib on renal function in healthy adult subjects. Twenty-four subjects were enrolled to receive Itacitinib SR3 600 mg BID and corresponding placebo for 8 days in a 2-period crossover design.
- **INCB 39110-122** open label, phase 1 trial to assess the effect of renal dysfunction on itacitinib PK (C_{max} and AUC_{0- ∞}) 300 mg itacitinib single dose PO following a medium-fat meal of 26 healthy healthy participants and participants with renal impairment or ESRD

Eight studies (INCB 39110-101, -102, -103, 113, 116, 118, 122 and 123) explored the PK, safety, and preliminary pharmacology of Itacitinib and contribute to the safety and clinical pharmacology data. The fourth study (INCB 39110-115) was completed in healthy adult subjects to assess the effects of Itacitinib on renal function. In completed clinical pharmacology studies, Itacitinib has been administered to 188 healthy adult subjects as a single dose, repeat single doses, or multiple doses for up to 10 days.

It was noted during the Phase 1 studies, which compared SR formulations, that the SR3 formulation exhibited the highest relative bioavailability compared with the IR formulation, and the least significant food-effect as measured by total mean exposure. Therefore, the 100 mg Itacitinib SR3 tablet formulation was selected for use in the Phases 1b and Phase 2 studies (noted as SR for these studies).

The Phase 2 program includes 2 completed proof-of-concept studies in subjects with active RA (INCB 39110-201) and psoriasis (INCB 39110-250) as well as 5 on-going clinical trials.

- **INCB 39110-201** was a Phase 2, double-blind, placebo-controlled, 2-part study of Itacitinib administered orally to subjects with active RA. In Part 1, a 28-day course of Itacitinib or corresponding placebo was administered orally to 3 staggered cohorts of 10 to 15 subjects each in doses of 400 mg BID, 100 mg BID,

and 100 mg QD. In Part 2, 28 days of oral administration were followed by an additional 56-day course of placebo or Itacitinib at the originally randomized dose, without regard to food.

- **INCB 39110-250** was a Phase 2a, double-blind, placebo-controlled, 28-day study of Itacitinib administered orally to subjects with stable, chronic plaque psoriasis. Itacitinib SR 100 mg tablets or corresponding placebo were administered orally as 100 mg QD, 200 mg QD, 200 mg BID, and 600 mg QD either 30 minutes before or 2 hours after a meal.

As of 30 APR 2021, 1699 unique study participants have been exposed to itacitinib, as follows:

- Healthy participants (543 participants)
- Itacitinib monotherapy (278 participants)

Adverse events that have been reported as very common ($\geq 1/10$) in healthy participants include headache and common ($\geq 1/100$ to $< 1/10$) neutropenia. In patients with underlying disease receiving monotherapy treatment, very common adverse reactions include anemia, pyrexia and headache. Adverse events reported by more than 10% of subjects receiving Itacitinib in the psoriasis study included nasopharyngitis.

Adverse events reported by more than 10% of subjects in the MF study included anaemia, fatigue, thrombocytopenia/platelet count decreased, nausea, diarrhoea, upper respiratory tract infection, constipation, cough, dyspnoea, peripheral oedema, pyrexia, dizziness, abdominal pain, night sweats, pain in extremity, arthralgia, contusion, headache, pruritus, vomiting, and increased bilirubin/hyperbilirubinemia. In the RA study, there were no TEAEs reported by more than 10% of subjects.

Events reported in $> 20\%$ of subjects in Study INCB 39110-116 and Study INCB 39110-203 in which Itacitinib was given in conjunction with chemotherapy were as follows: fatigue, anaemia, thrombocytopenia/platelet count, nausea, neutropenia/febrile neutropenia/neutrophil count decreased and agranulocytosis, pyrexia, diarrhoea, peripheral oedema, dysgeusia, headache, peripheral neuropathy, alopecia, cough, decreased appetite, dyspnoea, constipation, and dehydration. In lymphoid malignancies where Itacitinib was given in combination with INCB040093 or INCB050465, PI3K δ inhibitors, TEAEs observed in $\geq 10\%$ of subjects in Study INCB 40093-102 and Study INCB 40093-201 included nausea, cough, diarrhoea, thrombocytopenia/platelet count decreased, vomiting, pyrexia, fatigue, chills, night sweats, aspartate aminotransferase increased, neutropenia/neutrophil count decreased, constipation, decreased appetite, headache, back pain, dyspnoea, oropharyngeal pain, alanine aminotransferase increased, abdominal pain, anaemia, upper respiratory tract infection, asthenia, peripheral oedema, blood cholesterol increased, dizziness, muscle spasms, pain in extremity, rash, pruritus, tachycardia, blood creatinine increased, stomatitis, bronchitis, herpes zoster, sinusitis, hyponatremia, anxiety, dyspnoea exertional, hypotension, hypoxia, and urinary tract infection. Serious adverse events reported in more than 1 subject where Itacitinib was given in combination with INCB040093 included PCP (5 subjects), pyrexia (5 subjects), pneumonia (4 subjects), urinary tract infection (3 subjects), hypoxia (3 subjects), cardiac arrest (2 subjects), colitis (2 subjects), herpes zoster (2 subjects), respiratory failure (2 subjects), and syncope (2 subjects). For this combination treatment, certain classes of events are notable.

- **Infection:** Adverse events classified as infections occurred in 59.3% of subjects. Infections reported in more than 3 subjects included upper respiratory infection (14.8%), PCP (9.3%), urinary tract infection (9.3%), bronchitis (7.4%), fungal infection (7.4%), herpes zoster (7.4%), oral herpes (7.4%), and pneumonia (7.4%). Because of the increased risk of PCP in subjects receiving Itacitinib in combination with INCB040093, a standard prophylaxis regimen is now required for all subjects receiving this

combination. Since implementing this requirement, no additional cases of PCP have been observed in subjects receiving prophylaxis.

- Myelosuppression: Anaemia was observed in 14.8% of subjects, neutropenia was observed in 27.8% of subjects, and thrombocytopenia was observed in 33.3% of subjects.
- Hyperlipidaemia: Hyperlipidaemia has previously been noted in subjects receiving JAK inhibitors (Kontzias et al 2012). Six subjects (11.1%) were observed to have an increase in blood cholesterol that was greater than the upper limit of normal after receiving combination treatment with Itacitinib and INCB040093.

Serious AEs have been reported in RA (2 subjects), MF (28 subjects), solid tumours (25 subjects), and lymphoid malignancies (22 subjects). Itacitinib Investigator's Brochure v9_06FEB2017

Serious AEs reported in more than 1 subject in an individual study included the following:

- Pneumonia/bacterial pneumonia (3 MF subjects receiving monotherapy, 7 subjects receiving Itacitinib in combination with chemotherapy, and 3 subjects receiving Itacitinib in combination with INCB040093)
- *Pneumocystis jirovecii* pneumonia (5 subjects receiving Itacitinib in combination with INCB040093)
- Anaemia (5 MF subjects receiving monotherapy and 5 subjects receiving Itacitinib in combination with chemotherapy)
- Pyrexia (2 MF subjects receiving monotherapy, 2 subjects receiving Itacitinib in combination with chemotherapy, and 4 subjects receiving Itacitinib in combination with INCB040093)
- Congestive cardiac failure (3 MF subjects receiving Itacitinib monotherapy, 1 subject receiving Itacitinib in combination with chemotherapy)
- Chest pain (2 MF subjects receiving Itacitinib monotherapy)
- Acute renal failure (2 MF subjects receiving Itacitinib monotherapy, 1 subject receiving Itacitinib in combination with chemotherapy)
- Urinary tract infection (2 MF subjects receiving Itacitinib monotherapy, 1 subject receiving Itacitinib in combination with chemotherapy, 2 subjects receiving Itacitinib in combination with INCB040093)
- Respiratory failure (including acute and hypoxic respiratory failure) (3 subjects receiving Itacitinib in combination with chemotherapy, 2 subject receiving Itacitinib in combination with INCB040093)
- Gastrointestinal/upper gastrointestinal haemorrhage (2 MF subject receiving Itacitinib monotherapy, 3 subjects receiving Itacitinib in combination with chemotherapy)
- Febrile neutropenia (2 subjects receiving Itacitinib in combination with chemotherapy)

As a result of Itacitinib-mediated immunomodulation, whether administered alone or in combination with another agent, an increased incidence of infections could possibly occur. Strict clinical monitoring is indicated to identify and treat infections in study subjects should they occur. Because of the potential for myelosuppression, subjects should have hematologic parameters closely monitored during initial clinical studies. If there are clinically relevant declines in haematology parameters, therapy may be interrupted until resolution or discontinuation. Dose-escalation criteria regarding changes in haematological parameters should be specified in individual protocols. As Itacitinib also has the potential to cause WBC margination (ie, a transient decrease in ANC), assessment of haematology parameters should be performed before study drug administration at all applicable study visits.

Further details can be found in the investigator brochure.

1.3 Rationale

The aim of the study is to assess the effects of the JAK1 inhibitor Itacitinib as a second line treatment on patients with advanced inflammatory HCC. Inflammatory cells have been seen to produce cytokines that can activate STAT3 via the JAK pathway. This in turn enables them to become transcription factors and drive the expression of multiple genes important for cell activation, localisation, survival, and proliferation. It is therefore hypothesised that the ability of Itacitinib to inhibit the JAK pathway may cause a positive response in the patient's tumour.

1.4 Risk / Benefit Assessment

1.4.1 Potential Benefits

Patients may not directly benefit from enrolment on this trial, however, pre-clinical data has confirmed the ability of ITACITINIB in the Inhibition of JAK signalling and therefore may be therapeutic for the treatment of diseases such as MF, RA, psoriasis, GVHD, solid tumours, and B-cell malignancies, as JAKs serve to transduce extracellular signals from a number of cytokines and growth factors that are upregulated and thought to be involved in the pathogenesis of such conditions.

1.4.2 Potential Risks and their Management

Itacitinib affects the immune system. Therefore, subjects must be monitored closely and administration should be discontinued if there is evidence of clinically significant infection or cancer progression. For this population monitoring and treatment of elevated liver function values a hyperlipidaemia will be tailored as appropriate to the individual subject characteristics; cholesterol-lowering agents, such as 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors, should be used with caution, as these drugs are also associated with liver function abnormalities. The study is being reviewed by a steering committee.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Endpoint

| Objective | Endpoint |
|--|---|
| To assess the safety and tolerability of Itacitinib in patients with advanced hepatocellular carcinoma (HCC) | As assessed by adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. |
| <i>To assess the efficacy of Itacitinib by overall response rate (ORR)</i> | ORR defined as complete response, partial response, stable disease or progressive disease at 8 weeks post treatment according to modified RECIST criteria (mRECIST) version 1.1 |

2.2 Secondary Objectives and Endpoints

| Objective | Endpoint |
|---|--|
| To assess the efficacy of Itacitinib by progression free survival (PFS) | PFS, defined as time from study entry to first evidence of disease progression assessed by mRECIST v1.1 or death due to any cause. |
| To assess the efficacy of Itacitinib by overall survival (OS) | OS, defined as time from study entry to death due to any cause. |

2.3 Translational / Exploratory Objectives and Endpoints

| Objective | Endpoint |
|--|---|
| 1. To assess for presence of predefined JAK1 mutations in tumour tissue and correlate with treatment outcome | To assess for presence of predefined JAK1 mutations in tumour tissue (NGS) and correlate with treatment outcome (mRECIST) |
| 1. To assess for presence of predefined JAK1 mutations in ctDNA | To assess for presence of predefined JAK1 mutations in ctDNA (NGS) |
| 1. To correlate changes in pro-inflammatory cytokines with treatment response | To correlate changes in pro-inflammatory cytokines (multiplex cytokine bead array) with treatment response (mRECIST) |

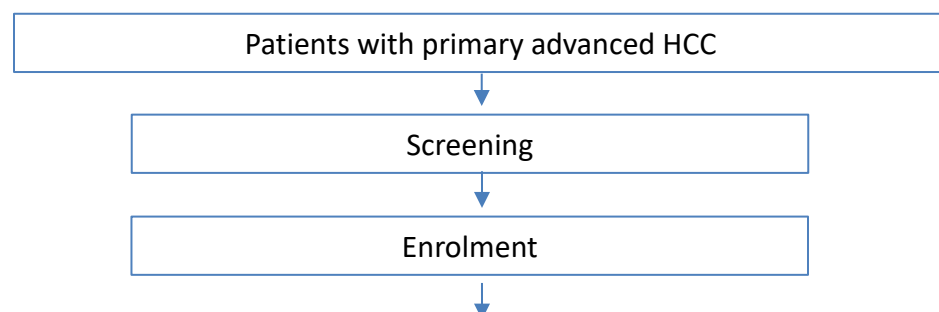
3 STUDY DESCRIPTION

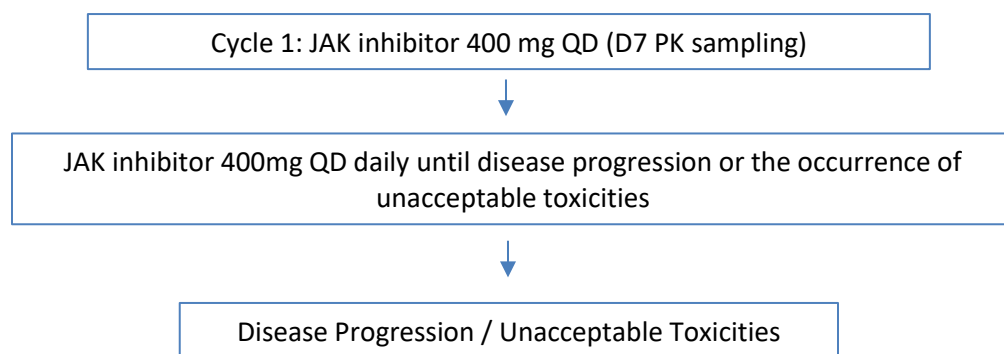
3.1 Design

This is a single arm phase Ib study to evaluate the effect of Itacitinib (a JAK1 inhibitor) in ~25 patients with advanced HCC. Eligible patients will receive Itacitinib every 400mg QD until disease progression, unacceptable toxicities or withdrawal of consent.

The first 10 patients will undergo attenuated pharmacokinetic profiling in cycle 1.

3.2 Study Flowchart





3.3 Study Population

3.3.1 Inclusion Criteria

Patients who meet all of the following inclusion criteria will be considered eligible for this study:

1. Aged 18 or over
2. Diagnosis of hepatocellular carcinoma. If primary diagnosis of HCC: diagnosis based on the following criteria:
 - cyto-histological criteria, OR
 - radiological criteria: Focal lesion >1 cm with arterial hypervascularization in 2 coincident imaging techniques (CT, MRI, or US), OR
 - combined criteria: one imaging technique showing a focal lesion 1-2 cm with arterial hypervascularization AND AFP levels >400 ng/mL, OR
 - combined criteria: one imaging technique showing a focal lesion >2 cm with arterial hypervascularization AND AFP levels >200 ng/mL
3. Progression or intolerance to first line therapy if child-Pugh A and B up to 7 points (in patients receiving anticoagulant therapy; Child-Pugh score up to 5 points; INR category not regarded for calculation of the Child-Pugh score)– N.B: Date of patients last dose of therapy must be more than 28 days before enrolment into this study
4. Child-Pugh B7 in patients who are treatment naive
5. ECOG Performance status 0, 1 or 2.
6. Adequate organ function as defined by:
 - Adequate hematologic function (ANC $\geq 1.0 \times 10^9/l$, platelet count $\geq 50 \times 10^9/l$, and hemoglobin $\geq 9g/dl$).
 - Serum creatinine concentration < 1.5 times the upper limit of normal (ULN) and/or creatinine clearance >60 ml/min
 - Bilirubin level < 1.5 X ULN
 - PT-INR/PTT < 1.5 x ULN
7. For women of child-bearing potential (defined as women who have not undergone surgical sterilization with a hysterectomy, and/or bilateral oophorectomy, and are not postmenopausal, defined as ≥ 12 months of amenorrhea) must have a negative serum pregnancy test within 14 days prior to the first study drug administration

Effective contraception must be used throughout the duration of the study and up to 30 days following

the last dose of the investigational medicinal product (IMP). Effective forms of contraception include complete abstinence from sexual intercourse, double barrier methods (condom with spermicide in conjunction with use of an intrauterine device or condom with spermicide in conjunction with use of a diaphragm), birth control patch or vaginal ring, oral, injectable, or implanted contraceptives and surgical sterilization (tubal ligation or vasectomy). Sperm and ova donation are prohibited during the duration of the study and 30 days after the last dose. 8. Written informed consent prior to initiation of any study procedures and willing and able to comply with the study schedule

3.3.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria will not be considered eligible for this study:

1. Previous treatment with:
 - Study medication, any other JAK1 inhibitor and/or known hypersensitivity to the study medication
 - An investigational agent within 28 days prior to start of study treatment
2. Serious concurrent medical or psychiatric illness, including serious active infection
3. Uncontrolled ascites
4. Uncontrolled hypertension
5. History of organ transplant (including prior liver transplant)
6. Diagnosis of HIV, congenital immune defect, any immunosuppressive therapy for autoimmune disease or inflammatory bowel disease
7. Patients with active or latent tuberculosis
8. Patients with active hepatitis C or active hepatitis B that requires treatment
9. Patients who have received a live vaccine 30 days or fewer prior to enrolment as well as patients who intend to receive live vaccination during study participation or for three months after last dose administration
8. Patients who have a history of unprovoked venous thromboembolism (VTE) prior to the diagnosis of malignancy
9. Pregnant or breast feeding women

Other clinically significant co-morbidities that could compromise the subject's participating in the study

3.4 Procedures and Measurements

3.4.1 Visit Schedule

Patients will be seen at screening then on day 1 and day 7 of cycle 1 and then every 4 weeks (from date of day 1) in clinic whilst on treatment. Treatment will continue until disease progression. When the patients stops treatment they will be required to attend a safety follow-up visit 28 days of treatment completion. For assessment details see table 1.

Table 1: Scheduled assessments

| Time point → Assessment ↓ | Screening | Cycle 1 | | Cycle 2 | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6 - Onwards | End of Treatment ¹⁰ | Safety Follow-up |
|---|-----------------|-----------------|-----------------|---------|---------|---------|---------|-------------------------------|-----------------------------------|--------------------------------|
| | Day -28 to 0 | Day 1 Week 1 | Day 7 Week 1 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 – Every 4 Weeks | | 28 days after last dose. |
| Informed Consent | X | | | | | | | | | |
| Medical History | X | | | | | | | | | |
| Demographics | X | | | | | | | | | |
| Height | X | | | | | | | | | |
| Vital Signs ¹ | X | X | X | X | X | X | X | X | X | X |
| Physical Exam | X | X | X | X | X | X | X | X | X | X |
| ECOG Performance Status | X | X | X | X | X | X | X | X | X | X |
| ECG ⁶ | X | | | | x | | | X ⁷ | | |
| Pregnancy Test | X ¹¹ | | | X | X | X | X | X | | |
| Haematology ² | X | X | X | X | X | X | X | X | X | X |
| Biochemistry ³ | X | X | X | X | X | X | X | X | X | X |
| Serology ⁴ | X | | | | | | | | | |
| Tumour Assessments (mRECIST) ⁵ | X | | | | X | | | X ⁵ | X ⁹ | |
| Archival Tissue or Fresh Frozen Research Biopsy – Mandatory | X | | | | | | | | | |
| Research Bloods ⁸ | X | | | | X | | | X ⁸ | X | |
| ctDNA sample ⁸ | X | | | | X | | | X ⁸ | X | |
| PK Sample ⁶ | | | X | | | | | | | |
| Itacitinib administration | | X | | X | X | X | X | X | | |
| Adverse Events | | X | | | | | | | | |
| Concomitant Medications | | X | | | | | | | | |

- Vital signs include weight, blood pressure, pulse, temperature
- Haematology includes: white blood cell count (WBC) with differential, haemoglobin (Hgb), haematocrit (Hct), and platelet count
- Biochemistry includes: Chem 7 (sodium [Na], potassium [K] chloride [Cl], bicarbonate [CO₂], blood urea nitrogen [BUN], creatinine [Cr], glucose), liver function tests (LFTs - ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin), LDH, total protein, calcium, phosphate, magnesium, and cholesterol.
- Serology includes: hepatitis B surface antigen, hepatitis B surface antigen antibody, hepatitis B core antibody, hepatitis C virus antibody, HCV-RNA load, HIV serology.
- CT Scans at baseline may be performed 28 days prior to study drug administration. Subsequent tumour assessments will occur every 8 weeks from first Itacitinib dose until progression or withdrawal.
- PK Samples only applicable for the first 10 patients and should be collected on day 7 prior to first dose of Itacitinib and at 1 hour, 2 hours and 4-8 hours post dose.
- ECG every 3 cycles from first Itacitinib dose until progression or withdrawal.
- Research Bloods & ctDNA to be collected every 8 weeks from first Itacitinib dose until progression or withdrawal.
- Tumour assessment only applicable if last measurement was more than 4 weeks.
- For all patients when they finish treatment, if this is at a cycle visit then end of treatment assessments are done in place of the cycle visit assessments.
- Serum test, 14 days before first study drug administration

3.5 Follow Up

Patients will continue treatment until:

- Disease Progression
- Unacceptable toxicities
- Patient decision / withdrawal of consent
- Investigator decision

4 TRIAL TREATMENT

4.1 IMP Administration and Schedule

Trial treatment must begin with 28 days of study enrolment. 400mg of Itacitinib will be administered QD;

The IMP is produced in the USA but shipped to Catalent Bathgate in the UK for distribution, each bottle has 35 x 100mg tablets. Study drug will be labelled in accordance with Good Manufacturing Practice (GMP), local regulatory requirements and all other applicable laws and regulations and QP released for the EU directly by Calatent Bathgate. Supplies of Itacitinib will be stored appropriately at the study site in the hospital pharmacy, where dispensing will also take place. IB will be used as Reference Safety Information (RSI).

4.2 Dose Modifications

4.2.1 Dose Interruptions

Clinically indicated dose interruptions of JAK-I are permitted for up to 14 days. If a treatment break continues for greater than 14 days the patient will need to withdraw from study.

4.2.2 Dose Reductions

Toxicities will be graded according to NCI-CTCAE version 4.03. Dose reductions are to be made according to the system showing the greatest degree of toxicity.

All patients will receive 400mg QD until the patient suffers from disease progression. Should any patients suffer from significant toxicity the dose can be reduced to 300mg QD.

| Toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|--------------------|---------------------------------|---------------------------------|---|---|
| Non-haematological | Continue at the same dose level | Continue at the same dose level | Withhold dose until toxicity is grade ≤ 1 , then resume treatment at the same dose level. If the patient experiences a second grade 3 toxicity, withhold dose until the toxicity is grade ≤ 1 , then reduce dose to 300mg QD and resume treatment. If there is no toxicity grade ≥ 1 after 28 days re-escalation to 400mg QD should be done for 28 days. Without further | Withhold dose until toxicity is grade ≤ 1 , resume treatment at reduced dose level of 300mg QD or discontinue at the discretion of the principal investigator. |

| | | | | |
|----------------|---------------------------------|---------------------------------|---|---|
| | | | aggravation of toxicity full dose can be continued. Generally the dose with toxicity grade ≤ 1 should be maintained. | |
| Haematological | Continue at the same dose level | Continue at the same dose level | Withhold dose until toxicity is grade ≤ 1 , then resume treatment at the same dose level. If the patient experiences a second grade 3 toxicity, withhold dose until the toxicity is grade ≤ 1 , then reduce dose to 300mg QD and resume treatment. If there is no toxicity grade ≥ 1 after 28 days re-escalation to 400mg QD should be done for 28 days. Without further aggravation of toxicity full dose can be continued. Generally the dose with toxicity grade ≤ 1 should be maintained. | Withhold dose until toxicity is grade ≤ 1 , resume treatment at reduced dose level of 300mg QD or discontinue at the discretion of the principal investigator. |

4.2.3 Study Withdrawal

A subject **must** be withdrawn from **study treatment** IF:

- The subject has experienced an unacceptable toxicity
- The subject is unwilling to continue receiving study treatment.
- The subject has experienced clinical deterioration/disease progression.
- In the opinion of the investigator, it is in the best interest of the subject not to continue receiving the study treatment.
- The subject becomes pregnant.
- Consent to receive treatment is withdrawn.
- Termination of the study by the sponsor.
- Termination of the study by the local health authority, IRB, or IEC.

A subject **may** be withdrawn from **study treatment** if, during the course of the study:

- Is found not to have met eligibility criteria; the subject would be withdrawn if the investigator, determines that the subject would not benefit from participation in the study due to the eligibility deviation.
- Is noncompliant with study procedures or study drug administration in the opinion of the investigator.

5. CONCOMITANT MEDICATIONS AND MEASURES

All concomitant medications and treatments must be recorded in the CRF. Any prior medication received up to 28 days before randomization will be recorded in the CRF. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the CRF.

5.1. Restricted Medications and Measures

- Inducers of CYP3A4 (Appendix A) may be used with caution, and investigators should seek other options if available.
 - Use of potent inhibitors of CYP3A4 (ketoconazole, clarithromycin, itraconazole, nefazodone or telithromycin, voriconazole or posaconazole, see Appendix A) and use of fluconazole should be avoided. If used, the itacitinib dose should be reduced from QID to BD with frequent complete blood count monitoring during the period of co-administration. Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole in the study.
 - Moderate CYP3A4 inhibitors (Appendix A) may be used with caution. Differences in individual sensitivity and variation in potency of inhibition of various CYP enzymes may result in the need for a reduced dose of itacitinib during a period of concomitant medication use. If used, the itacitinib dose may be reduced from QID to BD with frequent complete blood count monitoring during the period of co-administration.
- Systemic corticosteroid doses greater than the equivalent of 10 mg/day prednisolone are not permitted from the screening visit through the follow-up visit.

5.2. Prohibited Medications and Measures

- Use of any concurrent anticancer therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, or tumor embolization) other than those specified in the Protocol.
- Concomitant use of a JAK inhibitor
 - Concomitant use of immunosuppressive therapies
 - Live vaccines during the study and up to 3 months following the last dose of itacitinib
- Use of any investigational medication within 28 days or 5 half-lives, whichever is longer, prior to the first dose of study drug through the duration of study treatment is prohibited.
- St John's wort and rifampin are not permitted at any time during study participation.

6 ADVERSE EVENTS

6.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. *An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP*

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered. *All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.*

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (eg investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product). *When the outcome of the adverse reaction is not*

consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the SmPC which occur in a more severe form than anticipated are also considered to be unexpected.

Serious Adverse Event (SAE) or Serious Adverse Reaction: any untoward medical occurrence or effect that at any dose:

- **Results in death.**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation.**
- **Results in persistent or significant disability or incapacity.**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

6.2 Causality

Most adverse events and adverse drug reactions that occur in this study, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used in this study. The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigators. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

| Relationship | Description |
|------------------|---|
| Unrelated | There is no evidence of any causal relationship |
| Unlikely | There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment). |
| Possible | There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments). |

| | |
|-----------------------|--|
| Probable | There is evidence to suggest a causal relationship and the influence of other factors is unlikely. |
| Definitely | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. |
| Not assessable | There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship. |

6.3 Reporting Procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the study coordination centre in the first instance. A flowchart is given below to aid in the reporting procedures.

6.3.1 Non serious AR/AEs

All such toxicities, whether expected or not, should be recorded in the toxicity section of the relevant case report form and sent to the study coordination centre within one month of the form being due.

6.3.2 Serious AR/AEs

Fatal or life threatening SAEs and SUSARs should be reported on the day that the local site is aware of the event. The SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

SAEs

An SAE form should be completed and faxed to the study coordination centre for all SAEs within 24 hours. However, relapse and death due to a non study drug related condition and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

SUSARs

In the case of suspected unexpected serious adverse reactions, the staff at the site should:

Complete the SAE case report form & send it immediately (within 24 hours,), signed and dated to the study coordination centre together with relevant treatment forms and anonymised copies of all relevant investigations

Or

Contact the study coordination centre by phone and then send the completed SAE form to the study coordination centre within the following 24 hours as above.

The study coordination centre will notify the MHRA, REC, the Sponsor and the Funder (Incyte: SafetyReporting@incyte.com or via fax to (+)1-866-981-2057) of all SUSARs and SAEs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study.

Local investigators should report any SUSARs and /or SAEs as required by their Local Research Ethics Committee and/or Research & Development Office

6.3.3 Procedures for Reporting SAEs and Exposure to Study Drug During Pregnancy to the Funder, Incyte

As the Study is **interventional**, the Institution must report to Incyte the following, regardless of the Principal Investigator's causality assessment:

- i. all Serious Adverse Events (SAEs), and
- ii. Information regarding exposure to the Study Drug during pregnancy.
- a. Initial Reporting:
 - iii. Upon learning of an SAE or exposure to Study Drug during pregnancy that is required to be reported pursuant to Applicable Law, Institution shall complete and submit the Adverse Event Report Form or Pregnancy report form, as applicable, to Incyte within twenty-four (**24**) hours of learning of the event, via email to SafetyReporting@incyte.com or via fax to (+)1-866-981-2057.
 - iv. If critical or outstanding information is missing from the Adverse Event (or Pregnancy) Report Form or additional clarification is needed, Incyte shall submit a Data Clarification Form ("DCF") to the Institution/Principal investigator. In any case, Institution shall be solely responsible to respect of pharmacovigilance obligations and as such, will be the sole decision-making entity in case of disagreement.
- b. Follow-up Reporting:
 - i. When new information regarding an initially reported SAE or exposure to Study Drug during pregnancy becomes available, the Institution shall provide such follow-up information on a new or updated Adverse Event (or Pregnancy) Report Form within twenty four (24) hours of becoming aware of the information, via email to SafetyReporting@incyte.com or via fax to (+)1-866-981-2057.

Contact details for reporting SAEs and SUSARs

Rgit.ctimp.team@imperial.ac.uk

attention Dr Rohini Sharma

Please send SAE forms to: m.martinez@nhs.net

Tel: 0203 3133170 (Mon to Fri 09.00 – 17.00)

7 STATISTICAL CONSIDERATIONS

7.1 Sample Size and Power Calculation

This is a single arm phase Ib pilot study to evaluate the effect of Itacitinib in 25 patients with advanced HCC. The two primary outcomes for this study are safety and tolerability as well as overall response rate. The study will be powered on overall response rate as per the below. A trials steering committee will convene every 6 months to review safety and clinical data.

The Simon's minimax two-stage design will be used where the null hypothesis that the clinical benefit rate (CBR) is 0.05 will be tested against a one-sided alternative, defining the maximum unacceptable activity (p_0) for the experimental treatment as an overall response rate of 5% (33,34). Assuming the experimental treatment is able to achieve a minimal acceptable activity (p_1) of at least 25% of overall response rate so that the null hypothesis can be rejected, i.e. to test the alternative one-sided hypothesis with 90% power that the overall response rate (p_1) is greater than p_0 , at least 4 or more response patients with clinical benefit will have to be reported among the final sample size of 25 patients. In accordance with the Simon's minimax two-stage design, an interim comparison of activity will be conducted in the first stage at complete assessment of the primary efficacy endpoint for the first 15 patients accrued. For a 20% difference in response rate CBR (5% v 25%), at least 1 patient with overall response should have been observed among the first 15 patients. If there are 0 responses in these 15 patients, the study will be stopped. Otherwise, 10 additional patients will be accrued for a total of 25 and a second comparison will be made on the final sample size. This design yields a one sided type I error rate of 0.05 and power of 0.90 when the true response rate is 0.25.

7.2 Analysis Plan

The clinical data will be entered and stored in InForm™ database. Statistical analysis will be conducted using R version 3.0.1 and Stata version 14.

One interim analysis is planned as described above for the efficacy primary endpoint. A final analysis will be conducted at the end of the study. Analyses will include an intent to treat analysis including all patients enrolled and a per protocol analysis using all patients who complete the study without major protocol violations.

Histograms and boxplots will be used to check the distribution and possible outliers for continuous variables. Continuous variables that follow a normal distribution will be summarised using means and standard deviations. Skewed continuous variables will be summarised using medians and inter-quartile ranges. Categorical variables will be summarised using frequencies and percentages.

A separate statistical analysis plan will be prepared and finalised prior to database lock. Any deviation(s) from the final statistical plan in the final analysis will be described and justification will be given in the final report.

7.2.1 Analysis Plan

Due to sample size constraints, for the primary outcomes of assessing the safety and tolerability of Itacitinib and overall response rate, we will use descriptive measures such as frequencies and percentages.

All patients who receive at least one dose of study treatment will be included in the safety analysis set. The frequency of adverse events (AEs) will be assessed for severity (NCI CTCAE v4.03), expectedness, seriousness and causal relationship to study drugs(s). In addition, AEs will be summarised by toxicity type, impact on study drug(s) and by timing.

All efficacy data in the study will be analysed on an intention-to-treat (ITT) basis, regardless of treatment received. To be considered 'evaluable' for the primary efficacy analysis, a patient must have a week 8 tumour assessment or evidence of disease progression or death prior to week 8.

For quality of life measures, both means and standard deviations for continuous variables as well as frequencies and percentages for categorical variables will be used.

For the translational / exploratory endpoints, appropriate descriptive measures as well as univariate models will be shown as dependent on whether the relevant measure is categorical or continuous, whether the test is paired or not and whether is it normally or non-normally distributed as indicated below. Translational endpoints may not be included in the Clinical Study Report.

Univariate models will be performed for all demographic and other study variables, as statistically appropriate, as well as to test for confounding due to sample size constraints, with models such as Fisher's exact test or the Chi-square test utilised for categorical variables and t-tests or the Wilcoxon test (if the continuous variable does not follow a normal distribution) for continuous ones. For all estimates, 95% confidence intervals will be calculated.

8 REGULATORY ISSUES

8.1 CTA

This study has Clinical Trials Authorisation from the UK Competent Authority; MHRA.

8.2 Ethics Approval

The Study Coordination Centre has obtained approval from the Yorkshire & The Humber - Sheffield Research Ethics Committee (REC) and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions

8.3 Consent

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.4 Confidentiality

Participants' identification data will be required for the registration process. The Study Coordination Centre will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.5 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.6 Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.7 Funding

Incyte Corporation are funding this study

8.8 Audits And Inspections

The study may be subject to inspection and audit by Imperial College London under their remit as Sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

9 STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Hammersmith Cancer Research Office.

10 PUBLICATION POLICY

The results will be published once the study is complete

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Appendix A: Inhibitors and inducers of P450 CYP 3A4

| Precipitant | Therapeutic Class | Object ^a (oral, unless otherwise specified) | AUC _{ratio} | PMID or NDA # | Published |
|---|-------------------------------|--|----------------------|--------------------------|-----------|
| Potent CYP3A Inhibitors (yielding substrate AUCr > 5) | | | | | |
| indinavir /RIT | Protease Inhibitors | alfentanil | 36.5 | 19225389 | 2009 Mar |
| tipranavir/RIT | Protease Inhibitors | midazolam | 26.91 | 20147896 | 2010 June |
| ritonavir | Protease Inhibitors | midazolam | 26.41 | 20002087 | 2009 Dec |
| cobicistat (GS-9350) | None | midazolam | 19.03 | 20043009 | 2010 Mar |
| indinavir | Protease Inhibitors | varidenafil | 16.25 | NDA # 021400 | 2003 Aug |
| ketoconazole | Antifungals | midazolam | 15.9 | 8181191 | 1994 May |
| troleandomycin | Antibiotics | midazolam | 14.8 | 15536460 | 2004 Dec |
| saquinavir / RIT | Protease Inhibitors | midazolam | 12.48 | 19792991 | 2009 Oct |
| itraconazole | Antifungals | midazolam | 10.8 | 8181191 | 1994 May |
| voriconazole | Antifungals | midazolam | 9.63 | 21937987 | 2011 Nov |
| telaprevir | Antivirals | midazolam | 9.17 | NDA # 201917 | 2011 |
| mibefradil | Calcium Channel Blockers | midazolam | 8.86 | 14517191 | 2003 Oct |
| clarithromycin | Antibiotics | midazolam | 8.39 | 16432272 | 2006 Feb |
| lopinavir / RIT | Protease Inhibitors | aplaviroc | 7.71 | 16934050 | 2006 Sep |
| elvitegravir / RIT | Treatments of AIDS | midazolam IV | 6.8 | 18815591 | 2009 Jan |
| posaconazole | Antifungals | midazolam | 6.23 | 19302901 | 2009 Feb |
| nelfinavir | Protease Inhibitors | simvastatin | 6.07 | 11709322 | 2001 Dec |
| telithromycin | Antibiotics | midazolam | 6.0 | NDA# 021144 | 2004 |
| grapefruit juice DS ² | Food Products | midazolam | 5.95 | 12953340 | 2003 Aug |
| conivaptan | Diuretics | midazolam | 5.76 | NDA # 021697 | 2005 |
| nefazodone | Antidepressants | midazolam | 5.44 | 14551182 | 2003 Nov |
| saquinavir | Protease Inhibitors | midazolam | 5.18 | 10430107 | 1999 Jul |
| boceprevir | Antivirals | midazolam | 5.05 | NDA # 202258 | 2011 |
| Moderate CYP3A Inhibitors (AUCr ≥ 2 and < 5) | | | | | |
| fluconazole | Antifungals | midazolam | 4.93 | 16172184 | 2005 Oct |
| atazanavir / RIT | Protease Inhibitors | maraviroc | 4.9 | 18333863 | 2008 Apr |
| darunavir | Protease Inhibitors | saquinavir | 4.9 | NDA # 021976 | 2006 |
| erythromycin | Antibiotics | midazolam | 4.42 | 8453848 | 1993 Mar |
| diltiazem | Calcium Channel Blockers | midazolam | 4.06 | 21209240 | 2011 Nov |
| darunavir / RIT | Protease Inhibitors | sildenafil | 4.0 | NDA # 021976 | 2006 |
| dronedaron | Antiarrhythmics | simvastatin | 3.66 | NDA # 022425 | 2009 |
| atazanavir | Protease Inhibitors | maraviroc | 3.57 | 18333863 | 2008 Apr |
| aprepitant | Antiemetics | midazolam | 3.29 | 12891225 | 2003 Aug |
| casopitant | Antiemetics | midazolam | 3.13 | 20840445 | 2010 Oct |
| amprenavir | Protease Inhibitors | rifabutin | 2.93 | 11158747 | 2001 Feb |
| imatinib | Antineoplastic Agents | simvastatin | 2.92 | 14612892 | 2003 Nov |
| verapamil | Calcium Channel Blockers | midazolam | 2.92 | 8198928 | 1994 Mar |
| grapefruit juice | Food Products | midazolam | 2.39 | 10546919 | 1999 Oct |
| tofisopam | Benzodiazepines | midazolam | 2.36 | 17989974 | 2008 Jan |
| cyclosporine | Immunosuppressants | midazolam | 2.21 | 21753749 | 2011 Sep |
| ciprofloxacin | Antibiotics | sildenafil | 2.12 | 16372380 | 2005 Dec |
| schisandra sphenanthera | Herbal Medications | midazolam | 2.05 | 19552749 | 2009 May |
| cimetidine | H-2 Receptor Antagonists | midazolam | 2.02 | 6152615 | 1984 Sep |
| FK1706 | Central Nervous System Agents | midazolam | 2.01 | 19889885 | 2010 Feb |
| Weak CYP3A Inhibitors (AUCr ≥ 1.25 and < 2) | | | | | |
| tabimorelin | Hormone Replacement | midazolam | 1.93 | 12610745 | 2003 Feb |
| ranolazine | Cardiovascular Drugs | simvastatin | 1.89 | NDA # 021526 | 2006 |
| fosaprepitant (IV) | Antiemetics | midazolam | 1.76 | 21209230 | 2011 Dec |
| Seville orange juice | Food Products | felodipine | 1.76 | 11180034 | 2001 Jan |
| chlorzoxazone | Muscle Relaxants | midazolam | 1.68 | 11736864 | 2001 Nov |
| M100240 | Antihypertensive Agents | midazolam | 1.66 | 15051745 | 2004 Apr |
| fluvoxamine | Antidepressants | midazolam | 1.66 | 14551182 | 2003 Nov |
| ranitidine | H-2 Receptor Antagonists | midazolam | 1.66 | 6135440 | 1983 Jun |

| Precipitant | Therapeutic Class | Object ¹ (oral, unless otherwise specified) | AUC _{ratio} | PMID or NDA # | Published |
|---|--|--|----------------------|--------------------------|------------|
| Weak CYP3A Inhibitors (AUCr ≥ 1.25 and < 2) (continued) | | | | | |
| goldenseal | Herbal Medications | midazolam | 1.63 | 17495878 | 2008 Jan |
| clotrimazole | Antifungals | midazolam | 1.61 | 20233179 | 2010 Feb |
| tacrolimus | Immunosuppressants | midazolam | 1.61 | 21753749 | 2011 Sep |
| cilostazol | Antiplatelets | lovastatin | 1.56 | 10702889 | 1999 |
| peppermint oil | Food Products | felodipine | 1.55 | 12235445 | 2002 Sep |
| roxithromycin | Antibiotics | midazolam | 1.47 | 7995324 | 1994 |
| propiverine | Anticholinergics | midazolam | 1.46 | 16183781 | 2005 Dec |
| isoniazid | Antibiotics | triazolam | 1.46 | 6140941 | 1983 Dec |
| oral contraceptives | Oral contraceptives | triazolam | 1.44 | 6149030 | 1984 Nov |
| delavirdine | NNRTIs | indinavir | 1.44 | 9665503 | 1998 Jul 1 |
| atorvastatin | HMG CoA Reductase Inhibitors (Statins) | midazolam IV | 1.41 | 12911366 | 2003 Sep |
| tolvaptan | Vasopressin Antagonists | lovastatin | 1.41 | NDA # 022275 | 2009 |
| linagliptin | Dipeptidyl Peptidase 4 Inhibitors | simvastatin | 1.34 | 20497745 | 2010 June |
| resveratrol | Food Products | buspirone | 1.33 | 20716633 | 2010 Sept |
| lacidipine | Calcium Channel Blockers | simvastatin | 1.33 | 11259986 | 2001 Feb |
| cranberry juice | Food Products | midazolam | 1.33 | 19114462 | 2009 Mar |
| pazopanib | Kinase Inhibitors | midazolam | 1.32 | 20881954 | 2010 nov |
| nilotinib | Kinase Inhibitors | midazolam | 1.3 | NDA # 020068 | 2007 |
| AMD070 | Fusion Inhibitors | midazolam | 1.29 | 18362694 | 2008 Apr |
| alprazolam | Benzodiazepines | buspirone | 1.29 | 8300893 | 1993 Nov |
| amlodipine | Calcium Channel Blockers | simvastatin | 1.28 | 16097365 | 2005 Mar |
| bicalutamide | Antiandrogens | midazolam | 1.27 | 15509184 | 2004 |
| sitaxentan | Endothelin Receptor Antagonists | sildenafil | 1.27 | 20078609 | 2010 Jan |
| azithromycin | Antibiotics | midazolam | 1.27 | 8720318 | 1996 Feb |
| ginkgo | Herbal Medications | midazolam | 1.25 | 17050793 | 2006 Nov |

| Inducers | Object (oral, unless otherwise specified) | % ↓ AUC | % ↑ oral CL | Precipitant Regimen (oral) | Published | PMID or NDA# |
|--|---|--------------|--------------|--|-----------|--------------------------|
| Potent Inducers (AUC decreased by ≥ 80% or CL increased by more than 5 fold (400%)) | | | | | | |
| rifampin | budesonide | 99.7 | 36904.5 | 600 mg QD (7 days) | 2005 | 15726657 |
| mitotane | midazolam | 94.5 | Not Provided | maximum of 3.5 g TID (chronic therapy) | 2011 | 21220434 |
| avasimibe | midazolam | 93.5 | Not Provided | 750 mg/day (7 days) | 2003 | 12766253 |
| phenytoin | nifedipine | 89.5 | Not Provided | 200-450 mg/day (chronic treatment) | 1996 | 8917062 |
| carbamazepine | quetiapine | 86.6 | 643.1 | 200 mg TID (26 days) | 2006 | 16390352 |
| St John's Wort | midazolam | 80.0 | Not Provided | 300 mg TID (14 days) | 2006 | 16341856 |
| rifabutin | delavirdine | Not Provided | 458.0 | 300 mg QD (14 days) | 1997 | 9224961 |
| phenobarbital | verapamil | 76.6 | 400.9 | 100 mg QD (21 days) | 1968 | 3392664 |
| Moderate Inducers (AUC decreased by 50-80% or CL increased by 2-5 fold (100-400%)) | | | | | | |
| ritonavir and St. Johns wort | midazolam | 77.2 | Not Provided | ritonavir: 300 mg BID and SJW: 300 mg TID (14 days) | 2010 | 19924124 |
| tipranavir and ritonavir | saquinavir | 75.6 | Not Provided | tipranavir: 500 mg and ritonavir: 200 mg BID (14 days) | 2008 | 18176328 |
| bosentan | sildenafil | 69.0 | 239.8 | 62.5-125 mg BID (8 weeks) | 2005 | 15963102 |
| naftillin | nifedipine | 62.6 | 145.1 | 500 mg 4 times daily (5 days) | 2003 | 12814453 |
| [talvireline] | indinavir | 61.7 | 181.2 | 500 mg TID (14 days) | 1999 | 10516944 |
| efavirenz | simvastatin acid | 60.4 | Not Provided | 600 mg QD (15 days) | 2005 | 15980690 |
| modafinil | triazolam | 57.6 | 35.7 | 200-400 mg QD (28 days) | 2002 | 11823757 |
| etravirine | sildenafil | 56.7 | Not Provided | 800 mg BID (13.5 days) | 2008 | NDA# 022187 |
| Weak Inducers (AUC decreased by 20-50% or CL increased by less than 2 fold (100%)) | | | | | | |
| garlic | saquinavir | 44.7 | Not Provided | caplet of GarlPure BID (20 days) | 2002 | 11740713 |
| amprenavir | lopinavir | 43.0 | Not Provided | 700 mg BID (2-4 weeks) | 2005 | 15668538 |
| [troglitazone] | simvastatin | 37.7 | Not Provided | 400 mg QD (24 days) | 2001 | 11361054 |
| sorafenib | sirolimus | 36.9 | Not Provided | 200 mg BID (11 days) | 2010 | 21045832 |
| rufinamide | triazolam | 36.7 | 53.4 | 400 mg BID (11.5 days) | 2008 | NDA # 021911 |
| [pleconaril] | midazolam | 34.6 | 52.8 | 400 mg TID (6 days) | 2006 | 16467135 |
| ginkgo | midazolam | 33.7 | 52.6 | 120 mg BID (28 days) | 2008 | 18205997 |
| vinblastine | midazolam IV | 33.2 | 48.8 | not provided (4 cycles) | 2010 | 20959500 |
| nevirapine | indinavir | 32.5 | Not Provided | 200 mg QD (14 days), then BID (19 days) | 1999 | 10191212 |
| armodafinil (R-modafinil) | midazolam | 32.2 | 54.7 | 100-250 mg/day (31 days) | 2008 | 18076219 |
| prednisone | tacrolimus | 29.0 | Not Provided | 1.5 mg/kg/day | 2005 | 15787787 |