CANCER RESEARCH UK

Centre for Drug Development

A CANCER RESEARCH UK PHASE I TRIAL OF LY3143921 HYDRATE (A CDC7 INHIBITOR) GIVEN ORALLY IN ADULT PATIENTS WITH ADVANCED SOLID TUMOURS

Sponsor protocol number: CRUKD/17/004

EudraCT number: 2016-001245-80

Chief Investigator: Professor Richard Wilson

[redacted]

Sponsor: Cancer Research UK

[redacted]

PARTICIPATING INVESTIGATORS AND CENTRES:

Details of Principal Investigators and Investigational Sites are recorded on the Participating Investigators and Centres list in the Sponsor's Trial Master File.

VERSION HISTORY:

Version No.	Date of issue	Reason for update
1	01 Dec 2016	Initial version submitted for Regulatory and Ethics approval
2	19 Jan 2017	Update to clarify that if any changes are made to the dosing schedule, a substantial amendment will be submitted to the MHRA for approval (response to MHRA GNA)
3	26 Jun 2017	• Change in design of dose expansion cohorts to one stage without a formal efficacy analysis rather than the previously planned Gehan 2-stage design (response to REC review) • Removal of wording around retention of QP certification with every batch in the Pharmacy File as this is not an ICH GCP requirement • Clarification that LY3143921 hydrate capsule strengths ([redacted] mg and [redacted] mg capsules) are stated as LY3143921 content, not LY3143921 hydrate content • Addition of guidance around informed consent process • Clarification of visit windows for screening period • Modification to allow WHO status to be assessed in the preceding 24 hours of a visit • Addition of a visit window beyond Cycle 3 Day 1 and for 3 monthly follow-up visits • Correction of typographical error – change of PK serum to PK plasma • Correction of formatting errors throughout
4	05 Jan 2018	• Move to twice daily dosing permitted if necessary due to PK profiles observed in the initial cohorts • Single patient cohorts permitted above 120mg unless Grade 2 related toxicity is seen, due to PK profiles observed in initial cohorts • Clarification that PT and APPT results are required • Clarification of patient population • Additional requirement that patients meet inclusion criteria blood result ranges as the start of each cycle • Home blood pressure monitoring to be done three to six hours post dose, rather than at least six hours post dose.
5	21 Jan 2019	• Additional cohort of patients permitted to evaluate the effect of non-fasted drug administration on drug exposure

		• Additional DLT criteria of 'Any other related toxicity preventing administration of more than 25% of planned doses of IMP during Cycle 1' added. • Increase in the maximum number of patients to be recruited from 68 to 80. • Acceptable time window for radiological disease assessment increased from 3 to 5 days. • Change of address for the Chief Investigator. • Correction of typographical error in relation to febrile neutropenia dose limiting toxicity criteria. • Clarification of archival tumour specimen requirements.
6	23 Jan 2020	• Introduction of provisions to allow for further increased dose frequencies and intermittent dosing schedules to be investigated. • Confirmation of tumour types to be recruited to the expansion phase cohorts. • Clarification of tertiary objectives and endpoints. • Clarification of the pre-and post-treatment tumour biopsy requirements in the expansion cohorts. • Addition of pre and post treatment skin punch biopsy requirements in the expansion cohorts. • Change in exclusion criteria to allow patients on life-long hormone suppression treatment to be considered for the trial. • Clarification of inclusion criteria for patients taking oral anticoagulants. • Reduction in the frequency of clinic visits after Cycle 5 (escalation) and Cycle 3 (expansion) with agreement of Sponsor & CI. • Requirement for overnight BP monitoring on Cycle 1 Day 1 removed unless clinically indicated (expansion only). • Reduction in frequency of radiological disease assessment to every 3 cycles for patients who continue to receive IMP beyond 12 cycles. • Increase in the maximum number of patients to be recruited from 80 to 100. • Increase in study duration from 42 to 54 months. • Change of Sponsor address. • Clarification that planned hospital admissions for blood transfusions are exempt from SAE reporting.
7	19Mar2021	• Addition of a third expansion cohort to investigate an intermittent dosing schedule. • Reduction in the frequency of clinic visits after Cycle 2 (expansion) with agreement of Sponsor & CI. • Increase in the maximum number of patients to be recruited from 100 to 115. • Additional guidance on dose schedule changes and dose reductions added. • Requirement for take home anti-emetics added. • Requirement for phone assessment between Days 3-5 (Cycle 1 only) added.

		• Allowance for visits to be conducted with a ± 1 day window across all cycles. • Removal of tertiary assay to measure [redacted] • Addition of tertiary assay to measure [redacted] • Non-substantial: clarification on concomitant medications including COVID-19 vaccinations and required details to be collected. • Non-substantial: Section on Guidance for disruption to trial conduct added. • Administrative changes including clarification of primary objective wording and women of childbearing potential exclusion criteria wording in line with CTFG guidance and revised abstinence definition.
8	23Feb2023	• Updated haematological and biochemical threshold ranges that need to be met before a patient can continue treatment with LY3143921 hydrate. • Requirement for a formal clinical review and risk benefit assessment with written confirmation of the patients' willingness and understanding of potential risks of continuing to receive LY3143921 hydrate beyond 70 cycles. • Change in frequency of radiological scans and other investigations required post cycle 70 commensurate with extended treatment plan. • Preparation of an interim clinical study report including clinical data from all patients off study and from any patients continuing beyond 70 cycles at the point of an interim data lock followed by a final clinical study report when all patients are off study and final data listings are issued. • Non substantial: correction of 'LY3143921 hydrate' to 'LY3143921' when describing the substance measured in blood samples for the pharmacokinetic analysis. • Non substantial: removal of the term 'DLT' when describing adverse events emerging during the dose expansion phase of the trial that are a new intolerable or safety issue. • Non substantial: correction of 'maximum' to 'minimum' when describing time interval required to confirm that the criteria for attaining a response of stable disease are met.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
A	ABPI	Association of the British Pharmaceutical Industry
	AE	adverse event
	ALK	anaplastic lymphoma kinase
	ALP	alkaline phosphatase
	ALT	alanine aminotransferase
	ANC	absolute neutrophil count
	aPTT	activated partial thromboplastin time
	AST	aspartate aminotransferase
	AUC	area under the curve
B	BID	Bis die sumendum; twice daily
	BP	blood pressure
C	Cdc7	Cell division cycle 7
	CDD	Centre for Drug Development
	CDM	Clinical Data Manager
	[redacted]	[redacted]
	CI	Chief Investigator
	C_{max}	maximum observed plasma concentration
	cPARP	cleaved poly ADP ribose polymerase
	CR	complete response
	CRC	colorectal cancer
	CRA	Clinical Research Associate
	CRUK	Cancer Research UK
	CSM	Clinical Study Manager
	CSR	Clinical Study Report
	CT	computerised tomography
	CTA	clinical trial authorisation
	CTCAE	Common Terminology Criteria for Adverse Events
D	Day	calendar day
	DCF	data clarification form
	DLT	dose limiting toxicity
	DNA	deoxyribonucleic acid
E	ECG	Electrocardiogram
	ECHO	echocardiogram
	eCRF	electronic case report form
	EDC	electronic data capture
	EGFR	epidermal growth factor receptor
	ELISA	enzyme-linked immunosorbent assay
F	FDG	Fluorodeoxyglucose
	FU	Formulation Unit
G	GIT	gastrointestinal tract
	GCP	Good Clinical Practice
	GFR	Glomerular filtration rate
	GLP	Good Laboratory Practice
	GMP	Good Manufacturing Practice
H	h	Hour
	H&E	Hematoxylin and eosin
	Hb	Haemoglobin
	HCG	human chorionic gonadotropin
	HED	Human equivalent dose
	HGSOC	high grade serous ovarian cancer

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
	HIV	human immunodeficiency virus
	HPV	human papilloma virus
I	ICH	International Conference on Harmonisation
	IF	Immunofluorescence
	IHC	Immunohistochemistry
	IMP	investigational medicinal product
	ITF	Investigator Trial File
L	LHRH	luteinising hormone-releasing hormone
	LVEF	left ventricular ejection fraction
	LCMS	Liquid chromatography mass spectrometry
M	MAD	maximum administered dose
	MAP	Mean arterial pressure
	mCRC	Metastatic colorectal cancer
	mg	milligrams
	MIA	Manufacturing/importers authorisation
	min	minute(s)
	MHRA	Medicines and Healthcare Products Regulatory Agency
	MRI	magnetic resonance imaging
	mRNA	messenger ribonucleic acid
	MTD	maximum tolerated dose
N	NCI	National Cancer Institute
	NGS	Next Generation Screening
	NICE	National Institute of Health and Care Excellence
	nM	Nanomolar
	NSCLC	Non-small cell lung cancer
P	PBMC	Peripheral blood mononuclear cell
	PCR	Polymerase chain reaction
	PD	progressive disease
	PET	positron emission tomography
	PI	Principal Investigator
	PK	Pharmacokinetic
	PO	Taken orally
	[redacted]	[redacted]
	PR	partial response
	PSRB	Protocol and Safety Review Board
	PT	Prothrombin time
Q	QC	quality control
	QP	Qualified Person
R	RBC	Red blood cell
	REC	Research Ethics Committee
	RECIST	Response Evaluation Criteria in Solid Tumours
	RP2D	recommended Phase II dose
S	SAE	serious adverse event
	SD	stable disease
	SDV	source data verification
	siRNA	small interfering ribonucleic acid
	SOC	standard of care
	SOP	standard operating procedure
	SPC	Summary of Product Characteristics
	SUSAR	suspected unexpected serious adverse (drug) reaction
T	$t_{1/2}$	terminal elimination half-life

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
	T_{max}	time to reach C_{max}
	TID	Three times daily
	TK	tyrosine kinase
U	ULN	upper limit of normal
	USM	urgent safety measure
W	WFI	water for injection
	WBC	white blood cell
	WHO	World Health Organisation

PROTOCOL SIGNATURES

Sponsor Signature:

The Sponsor has read and agrees to the protocol, as detailed in this document. I am aware of my responsibilities as the Sponsor under the UK Clinical Trials Regulations[1], the guidelines of Good Clinical Practice (GCP)[2], the Declaration of Helsinki[3], the applicable regulations of UK law and the trial protocol. The Sponsor agrees to conduct the trial according to these regulations and guidelines and to appropriately direct and assist sponsor's staff who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Signed by the Director of the Sponsor's Centre for Drug Development at Cancer Research UK:

Name: Dr Nigel A Blackburn

Signature: [redacted]

Date: [redacted]

1 The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.

2 ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Step 5, adopted by CPMP July 1996.

3 WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and all subsequent amendments including Oct 2013.

PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the UK Clinical Trials Regulations[1], the guidelines of Good Clinical Practice (GCP)[2], the Declaration of Helsinki[3], the applicable regulations of the relevant NHS Trusts and the trial protocol. I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control, who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Investigator's Name: Richard H. Wilson

Name of site: [redacted]

Signature: [redacted]

Date: [redacted]

1 The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.

2 ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Step 5, adopted by CPMP July 1996.

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1 PROTOCOL SYNOPSIS

Full title: A Cancer Research UK Phase I trial of LY3143921 hydrate (a Cdc7 inhibitor) given orally in adult patients with advanced solid tumours

Short title: A Phase I trial of LY3143921 hydrate in solid tumours

Table 1: Clinical trial primary objectives and endpoints

Primary Objectives	Endpoints
To propose a recommended dose for Phase II (RP2D) evaluation by determining the Maximum Tolerated Dose (MTD) and schedule of LY3143921 hydrate	Determining the maximal dose at which no more than one patient out of up to six patients at the same dose level experience a highly probably or probably drug related dose-limiting toxicity (DLT) and determining the schedule of administration at which the MTD is established
To assess the safety and toxicity profile of LY3143921 hydrate	Determining causality of each adverse event (AE) to LY3143921 hydrate and grading severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.02

Full details of secondary and tertiary objectives can be found in section 3.1

Study Design: This is a multi-centre, dose escalation and expansion, first in human Phase I trial in patients with advanced solid tumours.

Study treatment: Patients will receive LY3143921 hydrate capsules orally for 21 days (one cycle) for up to 12 cycles. If the patient is showing benefit the patient may continue beyond 12 cycles in accordance with guidance in section 5.7. The starting dose will be 30 mg.

Patient Population: Patients with proven advanced or metastatic solid tumours will be entered into this trial. The patient population in the dose-escalation phase will be enriched for patients with tumours commonly associated with p53 mutation or loss of function (colorectal cancer (CRC), high grade serous ovarian cancer (HGSOC), non-small cell lung cancer (NSCLC, squamous cell variant), squamous carcinoma of the oesophagus, squamous carcinoma of the head and neck (human papilloma virus [HPV] negative [1]), urothelial cancer, breast cancer (triple negative type) and pancreatic cancer). In the dose expansion phase patients will be enrolled into three distinct cohorts: Cohort 1: patients with metastatic CRC; Cohort 2: patients with squamous NSCLC and Cohort 3: patients with solid tumours commonly associated with P53 mutation or loss of function. It is expected that between 40 and 115 patients will be required to complete this trial, the final number depending on the number of dose levels explored and numbers enrolled into the expansion cohorts.

2 INTRODUCTION

2.1 Background

Cell division cycle 7-related protein kinase (Cdc7), a serine-threonine kinase, is required to initiate deoxyribonucleic acid (DNA) replication, complete M-phase, and execute an Sphase- checkpoint in mammalian cells. Overexpression of Cdc7 has been associated with many cancers including primary breast, colon, and lung and pancreatic tumours [2-6]. Loss of Cdc7 function has been studied in various cancer cell lines using small interfering ribonucleic acid (siRNA) knockdown. Delay/arrest in the S phase of the cell cycle, followed by accumulation of nuclear damage and chromosomal fragmentation with eventual cell death was seen, independent of p53 expression [7, 8]. The expression of Cdc7 messenger RNA (mRNA) was shown to be significantly increased in colorectal cancer in comparison to normal colorectal tissues, which suggests Cdc7 may play an important role in the development and progression of colorectal cancer [2, 6]. In ovarian cancer, an increase in Cdc7 expression correlated with increase in tumour grade and accelerated cell cycle progression, and was able to distinguish between indolent and aggressive epithelial ovarian carcinoma [9]. It has previously been reported that p53 mutant cancers rely on the S-phase checkpoint and Cdc7 for survival [10]. This is supported by recent genome-wide analysis of p53 function, which suggests that p53 activation upon genotoxic stress enforces cell cycle withdrawal through repression of S-phase and G2/M genes including Cdc7 [11].

The study will enrich for those patients with tumours most likely to receive benefit. Our hypothesis is that cancers with p53 loss-of-function mutational status may be particularly sensitive to inhibition of Cdc7 [12]. The study will focus tumour types purported to have overexpression of Cdc7 and p53 mutations and functional loss including metastatic colorectal cancer (CRC) and high grade serous ovarian cancer (HGSOC), non-small cell lung cancer (NSCLC), particularly the squamous variant, squamous carcinoma of the oesophagus, squamous carcinoma of the head and neck (Human Papilloma Virus (HPV) negative), urothelial cancer, triple negative breast cancer and pancreatic cancer [1, 2, 13-16].

Eligible patients will be those for whom there is no standard treatment option, for whom standard care options are of limited utility or those refractory to standard therapies, however some patients may elect for a Phase I trial before use of third line conventional treatment, which often has limited utility. For patients with metastatic CRC (mCRC), this could be in a setting after second-line therapy, for whom epidermal growth factor receptor (EGFR) inhibitors are inappropriate or unavailable. For HGSOC, this could be patients who were resistant or intolerant to platinum therapy. For NSCLC this may be in patients who have progressed after platinum-combination therapy and second-line docetaxel, or after EGFR inhibitors in EGFR tyrosine kinase (TK) mutation positive patients.

2.1.1 Colorectal Cancer

Colorectal cancer (CRC) is the third most common cancer in both males and females in the UK.

During 2013, there were 44,100 new cases of colorectal cancer diagnosed in England: 23,000 in men and 18,200 in women. Globally an estimated 1.36 million new cases occurred in 2012 [17]. The crude incidence rate shows that there are around 75 new bowel cancer cases for every 100,000 men in the UK and around 56 for every 100,000 women [17]. Almost 6 in 10 (58%) bowel cancer cases in the UK each year are diagnosed in people aged 70 and over (2011-2013). Age-specific incidence rates increase sharply from around age 50, with the highest rates in the 85 years and older age group [17]. Over the last decade, bowel cancer incidence rates have increased by a twentieth (5%) in the UK [17].

Colorectal cancer includes colon cancer and rectal cancer; almost two-thirds (66%) of all bowel cancers are cancers of the colon and over one-third (34%) are cancers of the rectum (including the anus) [18]. More than 95% of diagnosed colorectal cancers are adenocarcinomas [19].

The population of patients with metastatic colorectal cancer includes both those who present with metastatic disease and those who develop metastatic disease after their initial presentation and surgery. Estimates of people presenting with mCRC range from 20% to 55% of new cases. Out of those who have undergone surgery for colorectal cancer with apparently complete excision,

approximately 50% will eventually develop advanced disease and distant metastases (typically presenting within two years of initial diagnosis). The five year survival rate for mCRC is 12%[20].

The most frequent site of metastatic disease is the liver. In up to 50% of patients with metastatic disease, the liver may be the only site of spread. For these patients surgery provides the only chance of longer-term survival. Approximately 10% of patients with mCRC present with potentially resectable liver metastases and for approximately 14%, chemotherapy may render unresectable liver metastases operable.

Chemotherapy for advanced and metastatic CRC is based around oxaliplatin and irinotecan in combination with fluoropyrimidines. Combinations currently include [21]:

- FOLFOX (folinic acid plus fluorouracil plus oxaliplatin) as first-line treatment then single agent irinotecan as second-line treatment or
- FOLFOX as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment or
- XELOX (capecitabine plus oxaliplatin) as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment.
- Cetuximab (for KRAS and NRAS wild type CRC) with chemotherapy in potentially resectable liver only metastatic disease.

While the VEGF-A targeting monoclonal antibody Bevacizumab is licensed for use with chemotherapy in both first- and second-line palliative treatment of mCRC, it is not currently funded in the NHS [22]. Similarly, Aflibercept, a fusion protein targeting VEGF-A, B and C is licensed for use with FOLFIRI in second-line, but is not currently funded [23]. Regorafenib, an oral multi-kinase inhibitor principally targeting angiogenesis is licensed for use in the refractory third-line setting is not currently funded [24]. Lonsurf (TAS-102) is a fixed dose combination of trifluridine (targeting thymidylate synthesis and DNA) and tipracil (a thymidine phosphorylase inhibitor which prevents rapid degradation of trifluridine) is licensed and has recently been approved for use in the UK in the chemorefractory third-line setting [25]. Raltitrexed can also be considered for patients with advanced colorectal cancer who are intolerant to 5-fluorouracil and folinic acid, or for whom these drugs are not suitable (for example, patients who develop cardiotoxicity). Otherwise, treatments for advanced CRC are mainly palliative and aim to increase both the quality of the patient's remaining life while controlling symptoms. Based on this there is clearly an unmet need for effective therapies for patients with inoperable metastatic CRC.

2.1.2 Non-Small Cell Lung Cancer

Lung cancer is the second most common cancer and a major cause of cancer-related deaths globally. In 2013, there were 45,525 new cases of lung cancer in the UK: 24,481 (54%) in males and 21,044 (46%) in females ([26]). Non-small cell lung cancer (NSCLC) represents approximately 85% of all cases [27]. A minority of patients present with early stage disease amenable for surgery which is the only treatment which offers long term remission. More than half of the patients are still diagnosed with advanced metastatic disease at the time of presentation and have a poor prognosis. The two year survival rate is only 5% with median survival between eight and 10 months [28]. For patients with metastatic disease the first line treatment option is usually systemic therapy and symptom management including radiotherapy. The choice of first line therapy depends on performance status, histology and predictive molecular markers. Advances have been made in the design and development of agents directed against novel molecular targets in NSCLC, including the epidermal growth factor receptor (EGFR) tyrosine kinase activity, anaplastic lymphoma kinase (ALK) gene rearrangements and extracellular regulated kinases (ERK) that have the potential for improving clinical outcome. Crizotinib was approved in 2013 and ceritinib in 2014 for the treatment of patients with metastatic NSCLC whose tumours are ALK-positive, however this only represents 3-7% of patients. Lung cancer has also recently emerged as a new target of immune-based therapies with nivolumab approved and pembrolizumab currently recommended for approval for the treatment of advanced (metastatic) squamous NSCLC that has failed chemotherapy. These drugs have very recently shown improved outcomes in RCTs against platinum-containing chemotherapy in the first-line setting. In the KEYNOTE-024 trial, there was significantly prolonged PFS and OS for pembrolizumab against chemotherapy in patients with advanced NSCLC and high PD-L1 expression [29]

While newer targeted agents certainly improve outcome for some NSCLC patients, for the majority long term and durable disease control is yet to be achieved and there remains a large unmet medical need for new therapy options for many NSCLC patients.

2.1.3 High Grade Serous Ovarian Cancer

Every year, within the UK, around 6,800 women are diagnosed with ovarian cancer [30]. Due to the non-specific symptoms, 70% of cases are diagnosed at an advanced stage, so the prognosis is generally poor, with an overall five year survival rate of less than 35%. Despite the relatively poor overall survival rates for ovarian cancer, there has been a two-fold increase in survival over the last 30 years [30] but there are still limited therapeutic options for advanced (stage II-IV) ovarian cancer (first line and recurrent) [31]. Current treatment options include:

- Paclitaxel is recommended in combination with a platinum-based compound or platinum-based therapy alone (cisplatin or carboplatin) are offered as alternatives for first-line chemotherapy (usually following surgery)

And for recurrent disease:

- Paclitaxel in combination with platinum or as monotherapy
- Pegylated liposomal doxorubicin hydrochloride (PLDH) as a monotherapy or in combination with platinum
- Olaparib for relapsed, platinum-sensitive ovarian, fallopian tube or peritoneal cancer who have BRCA1 or BRCA2 mutations and whose disease has responded to platinum-based chemotherapy if certain criteria are met.

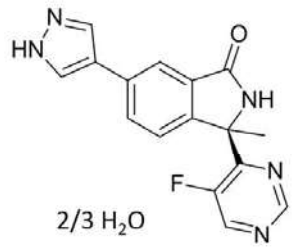
Adding bevacizumab to chemotherapy has also been shown to increase the time to disease progression and may improve survival [31].

2.2 Investigational medicinal product

LY3143921 hydrate is a potent inhibitor of cell division cycle 7 (Cdc7) developed by Eli Lilly. The primary scientific rationale behind the proposed trial is that some Cdc7 positive tumours may be sensitive to Cdc7 inhibition. Non-malignant cells do not express elevated levels of Cdc7 and are resistant to Cdc7 inhibition [2]. Furthermore, p53 mutant cancers rely on the S-phase checkpoint and Cdc7 for survival [10] and those cancers with p53 loss of- function mutational status may be particularly sensitive to inhibition of Cdc7 [10, 12]. Therefore the study will focus on tumours more likely to have mutational status in p53 such as metastatic colorectal cancer (CRC), high grade serous ovarian cancer (HGSOC) and squamous non-small cell lung cancer (NSCLC). For additional information concerning LY3143921 hydrate, refer to the Investigator Brochure.

2.2.1 Structure of LY3143921 hydrate

Figure 1: structure of LY3149321 hydrate (1*H*-Isoindol-1-one, 3-(5-fluoro-4-pyrimidinyl)-2,3- dihydro-3-methyl-6-(1*H*-pyrazol-4-yl)-, (3*R*)-Hydrate

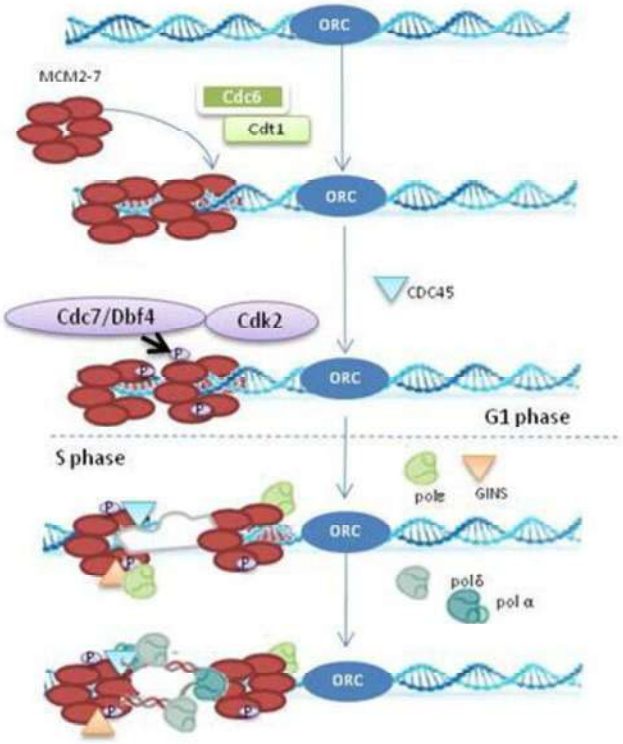


2.2.2 Mechanism of action of LY3143921 hydrate

LY3143921 hydrate, a selective inhibitor of Cdc7, a protein kinase subunit of Dbf4-dependent kinase (DDK), is best characterised as a regulator of DNA replication and repair, homologous recombination and chromosome segregation in mitosis and chromatin modification [32].

The cell division cycle 7 (Cdc7) is a serine threonine kinase that is essential for the progression through the cell cycle. Cdc7 together with Cdk2 are responsible for the transition from G1/S transition and the S phase progression [32]. Cdc7 and CdK2 are responsible for phosphorylating minichromosome maintenance complex (MCM) complex, which leads to the loading of other accessory factors including DNA polymerases so that active replication forks are generated which ultimately leads to the semiconservative replication of DNA and the progression through the S-phase into the M phase (**Figure 2**). In addition, to its roles in the S-phase of the cell cycle, Cdc7 and its activation subunits have been implicated in accurate chromosomal segregation during cytokinesis [33]. Cohesins, protein complexes responsible initially for protecting and later the separation of sister chromatids during cell division are tethered to replicating complex in Cdc7-dependent manner [33].

Figure 2: The role of Cdc7 in DNA replication



DNA replication is first initiated by the binding of ORC (origin recognition complex) to replication origins. With the co-operation of both Cdc6 and Cdt1, MCM (minichromosome maintenance complex) is delivered to the ORC. Both Cdc7 and Cdk2 phosphorylate elements of the MCM complex (N-terminal tails of MCM2, MCM4 and MCM6) which lead to loading of other accessory factors such as Cdc45 and a second helicase-activating protein (GINS) complex. Active replication forks are then generated by association of 3 DNA polymerases that ultimately lead to the semiconservative replication of DNA. Based on [34]

2.3 Safety considerations for the proposed trial

The information presented in the following sections was current at the start of the clinical trial. Please refer to the current version of the LY3143921 hydrate Investigator's Brochure (IB) for up to date information.

2.3.1 Non-clinical pharmacology

All non-clinical or clinical pharmacology studies were conducted with either the free base of LY3143921 or LY3143921 hydrate. LY3143921 and its hydrate are equipotent, selective inhibitors of Cdc7, in biochemical assays. LY3143921 and its hydrate demonstrated [redacted] over the next kinase, [redacted] Inhibition of Cdc7 was also measured in [redacted], measured as inhibition of the [redacted] at [redacted] concentrations [redacted] and had a [redacted] selectivity over other targets tested. LY3143921 demonstrated [redacted] and the [redacted] in a variety of cancer cell lines [redacted] with [redacted] within a [redacted] time frame. Several [redacted] and [redacted] cell lines demonstrated [redacted].

Human colorectal xenograft flank tumour [redacted] model [redacted] cell line) was used to ascertain the correlation between plasma exposure, dose and inhibition of [redacted] within tumours (Table 2). In vivo tumour [redacted], refer to section 2.3.2) which is similar to [redacted]

Table 2: Correlation between Dose, exposure and [redacted]

[redacted] post-dose	[redacted] Dose	HED	Plasma concentration [redacted] post-dose	
	mg/m²	Mg	ng/mL	µM
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

HED, human equivalent dose based on 60 kg human

To confirm that LY3143921 inhibition of Cdc7 was mediated by cell cycle arrest and eventual apoptosis, [redacted] which accumulates in G2/M and the apoptotic marker cleaved [redacted] were measured in [redacted] in a repeat dose study. Western blots revealed [redacted] and [redacted] and [redacted] in comparison to vehicle at both [redacted] and [redacted] post-dose, indicative of Cdc7 target inhibition, G2/M arrest and apoptosis via Caspase 3 activation.

In vivo, oral administration of LY3143921 showed stable disease and regression in [redacted] human xenograft flank tumour models representing [redacted] (**Table 3**). The minimum effective dose being [redacted] given [redacted] times a day [redacted] (**Table 3**) which [redacted] based on allometric scaling. Complete regression was seen at [redacted] at [redacted] was associated with continuous [redacted]

Table 3: Summary of LY3143921 anticancer activity in vitro and in vivo against [redacted] tumours

[redacted]	In vitro	In vivo efficacy
[redacted]		

Mouse strains were one of the following: [redacted] and mean tumour volume [redacted] dependent on tumour type. Positive values are [redacted] = (final tumour volume - baseline tumour volume)/ (final control volume – baseline control volume). Negative values are % regression = final volume - baseline volume / baseline volume. ND not determined. Statistical significance * p<0.05; ** p<0.01; *** p<0.001. Experiments with the same study no were [redacted] mplanted on the right to reduce animal numbers. [redacted] tumours; regression, orange tumours; cytostasis, red tumours less sensitive. [redacted]

LY3143921 hydrate anti-tumour activity was also evaluated in PDX models of [redacted] tumours [redacted] and [redacted] LY3143921 hydrate administered at [redacted] produced stable disease [redacted] Δ[redacted] to complete regression in approx. [redacted] of [redacted] tumours respectively (Figure 3). [redacted]

Figure 3: LY3143921 hydrate vs SOC across [redacted] patient derived [redacted]

LY3143921 hydrate was administered orally [redacted] twice a day for [redacted]. Water fall plot is representative of Median % response of 3 measurements. Compete regression [redacted], partial response is up to [redacted], stable disease is up to [redacted], and progressive disease is [redacted] Δ[redacted] (percent change of treated groups to control group)

In addition, a nude rat [redacted] xenograft model produced [redacted] than the mouse xenografts models with [redacted] correlating to a C_{max} and area under the curve (AUC) of [redacted] and [redacted] respectively and produced [redacted] regression (see section 2.3.2). Regression [redacted] was seen at [redacted], PO [redacted] correlating to C_{max} and AUC of [redacted] and [redacted], this was associated with a [redacted] inhibition [redacted] hours post administration dropping to [redacted] at [redacted] Oral administration of [redacted] mg/kg once daily [redacted] produced [redacted] regression, with continuous exposure above [redacted] (trough level) which was associated with [redacted] inhibition of [redacted] for [redacted] hours.

2.3.1.1 Secondary/Safety pharmacology

No significant activity was seen below [redacted] and LY3143921 had an IC_{50} above the highest dose evaluated [redacted] at the [redacted]. These micromolar exposures are unlikely to be clinically achievable due to the free fraction in humans predicted to be [redacted]

Safety pharmacology was assessed in stably transfected [redacted], non-Good Laboratory Practice (GLP) [redacted] In addition, respiratory and neurological parameters were evaluated in [redacted] and cardiovascular endpoints in [redacted] (Table 4).

Table 4: Summary table of primary pharmacodynamics and safety pharmacology

Min minimal effective dose, HED human equivalent dose based on allometric scaling of for [redacted], BP blood pressure; HR, heart rate; QTCi, individually correct QT interval, BID twice daily dosing, TID thrice daily dosing, [redacted], PDX patient derived xenograft, ND not determined, NA not applicable

Species		[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

No respiratory or neurological parameters were affected [redacted]. In vitro the IC_{50} at the [redacted] and [redacted] rate was seen in [redacted] studies in dose dependent manne[redacted] Dose dependent [redacted] was seen in [redacted] in a GLP study with an onset of ≥ [redacted] ranging from [redacted] to [redacted] and all effects were [redacted]. Therefore, although the [redacted] identified in this study may present a clinical risk it is likely that they will only present at exposures near the maximum tolerated dose. A clinical mitigation programme has been developed to manage the potential cardiovascular risks that might be presented by exposure to LY3143921 hydrate.

2.3.1.2 Summary

In summary, therapeutic effects were seen [redacted] producing [redacted] xenografts. Exposure levels [redacted] produced inhibition of Cdc7 above [redacted]. In the rat model a dose dependent therapeutic effect was seen at [redacted] A non-GLP cardiovascular [redacted] study saw [redacted] In non-GLP [redacted] studies dose dependent [redacted] effects were seen at [redacted], and [redacted] which were associated with plasma C_{max} [redacted]. Furthermore, in the GLP study dose dependent effects [redacted] on [redacted] and [redacted] were seen at [redacted] associated with C_{max} [redacted]. Clinically, doses above [redacted] could produce [redacted] and [redacted], however due to the difference in plasma protein binding in [redacted] and humans this dose maybe higher. Efficacy on the basis of the [redacted] studies may be expected at [redacted] A clinical mitigation programme has been developed to manage the potential cardiovascular risks that might be presented by exposure to LY3143921 hydrate.

2.3.2 Pharmacokinetics

The plasma protein binding of LY3143921 was comparable between [redacted] and [redacted] and lower in [redacted] Human plasma protein binding is predicted to be higher than the preclinical species [redacted] as measured in human plasma. This could have a clinical implication for the dose escalation and maximum tolerated dose as total exposure clinically could potentially be higher than those seen in the preclinical species owing to a predicted lower free fraction in humans due to the differences in protein binding. The PK properties of LY3143921 were evaluated in [redacted]. The in vitro membrane permeability of LY3143921 was [redacted] and [redacted], from the PK parameters in the preclinical species [redacted]™ [redacted] predicted the human fraction absorbed to be [redacted].

All preclinical species had a [redacted]. High [redacted] was seen in all species with the exception of the [redacted] which may explain the [redacted] doses required to produce efficacy in the [redacted] in comparison to the [redacted] xenografts.

In a repeat dose toxicity studies with LY3143921 hydrate there was [redacted] difference in the exposure for the [redacted]. Exposure in [redacted] approximately linearly with [redacted] and was maintained for [redacted] on [redacted]. [redacted], however this had little impact on [redacted] or other saturable components and accumulation was considered [redacted]. In vitro metabolism of LY3143921 was assessed in [redacted]. Metabolism was considered to be [redacted] in all species with no [redacted]. In vivo in [redacted] an [redacted] was seen and was not more than [redacted] of the parent at all time points measured in both species. This would indicate that [redacted] were seen and therefore are not expected clinically.

Preliminary studies would indicate that the primary route of elimination in [redacted] was [redacted], but [redacted] of the dose) was significant compared to the [redacted] Systemic clearance in [redacted] did not increase when [redacted] was co-administered indicating negligible contribution of [redacted]. Overall, metabolism was through a [redacted] with the parent being the [redacted] in all in vitro and in vivo studies. [redacted] also exhibited [redacted] of LY3143921 hydrate with [redacted] metabolism of the [redacted]

may take the same route as preclinical species. The excretion pathway in humans is hard to predict as [redacted] to be significant in [redacted], whereas renal was the most important clearance pathway for [redacted] If biliary clearance is substantial in humans there may be a potential for hepatic recirculation which will be reflected by clinical PK parameters such as half-life. A full PK profile in patients will be taken over 72 hours prior to commencing a full cycle and the dosing regime will be subject to change dependent on emerging data.

Investigation into the reversible inhibition of human liver microsomes [redacted] however it is unlikely free exposure levels will reach this concentrations clinically with the exception of [redacted] patients taking co-medications metabolised through CYP2C19, 2C9 and/or CYP3A4 will be carefully monitored. In addition, LY3143921 hydrate did not display time-dependent inhibition of [redacted] and there was also [redacted].

LY3143921 hydrate is a [redacted]). Consequently, the observed human half-life will be dependent upon the level of protein binding, metabolism and excretion. Pharmacokinetic (PK) modelling has predicted that median human clearance will be [redacted]

2.3.3 Toxicology

A program of in vivo and in vitro pre-clinical safety evaluation studies has been conducted to support the clinical use of LY3143921. All toxicity studies with the exception of the preliminary dose finding study in [redacted] (4 days repeat dose) used LY3143921 hydrate and the GLP studies were conducted with the batch of LY3143921 hydrate intended for the clinical trial (PT-C13070116-DF14001M) with the exception of the phototoxicity (The toxicology package contains in vitro toxicology assessments on bone marrow, corneal irritation and phototoxicity as well as an in vivo acute dermal study in r[redacted] multiple dose oral studies in [redacted]s up to one month duration, and an in vitro genetic toxicology study. The target tissue for LY3143921 induced toxicities were [redacted] and to a lesser extent other highly replicating tissues such as the [redacted] with the [redacted] (Table 5). In the [redacted] GLP study, the dosing was staggered [redacted] Therefore, the dose level was lowered to [redacted] from day 6 (therefore the [redacted] allocated to the highest dose evaluated were referred to [redacted]. In the [redacted] study the MTD was set at [redacted], based on reversible findings in the [redacted], which equates to a [redacted]. In the [redacted] GLP study the MTD was [redacted] and the highest dose tested was [redacted] HED for 60 kg body weight adult.

In the [redacted] GLP study all finding were reversible with the exception of [redacted] was seen in the [redacted]g GLP study in [redacted] only one male at the top dose showed [redacted]. In the [redacted] 14 day study [redacted] was seen in [redacted] dosed at [redacted] (60 mg/m^2/day); [redacted] was noted, [redacted] was seen In the [redacted] study (up to [redacted]le but only seen [redacted] indicating [redacted] the exposure of the [redacted] was seen at the [redacted] MTD dose with [redacted] correlates, [redacted] was seen in the recovery animals. However in [redacted] study minimal [redacted] was seen [redacted] although [redacted] were seen in the [redacted] the exposure levels at this dose were [redacted] than the [redacted] in the 14 day non-GLP study [redacted]. When [redacted] were administered [redacted] doses [redacted] in the non GLP studies the [redacted] that administration of LY3143921 hydrate may produce [redacted]

[redacted] at [redacted] was not seen in the [redacted] GLP study but there was evidence of [redacted] at the end of the dosing period which was [redacted] the recovery period. In non GLP studies [redacted] ≥ [redacted]. Decreased [redacted] accompanied [redacted] and were deemed to be at least in part due to [redacted] Changes in [redacted] were detected in both [redacted]. In the [redacted] was present in the [redacted] and [redacted] at [redacted] no [redacted] correlates were observed. In [redacted] studies [redacted] changes in [redacted] were seen in [redacted], with [redacted] in a subset of [redacted] and [redacted] were observed at all doses in GLP and pilot [redacted] phase period. [redacted] at doses above [redacted] was also seen [redacted]

[redacted] and [redacted] and [redacted] have not been performed for LY3143921 hydrate. [redacted] to LY3143921 hydrate has been performed, however, the intended clinical route of administration is oral and dosing via this route has been examined during toxicity studies. The [redacted] of LY3143921 hydrate was assessed in a GLP [redacted] in [redacted] and [redacted] LY3143921 hydrate did [redacted] in this study.

2.3.3.1 Summary of non-clinical toxicology data

Target tissues associated with administration of LY3143921 hydrate were [redacted] in both preclinical toxicology species used in GLP and non GLP studies. In the GLP studies [redacted] was the highest dose tested in the [redacted] with no adverse signs in the live phase or recovery animals, therefore the MTD was not reached and the [redacted] had [redacted] [redacted] respectively. In non-GLP studies onset of toxicity in some animals was [redacted] which produced a similar C_{max} [redacted] to the GLP studies, however due to the twice daily dosing AUC was [redacted] fold higher [redacted], the number of animals affected and severity of toxicity increased with increasing exposure [redacted] and the extent of recovery was not assessed in this non-GLP study.

In the [redacted] GLP study the majority of the effects were reversible with the exception of some [redacted] and [redacted], with the MTD set [redacted], the exposure levels at this dose were C_{max} and $AUC_{0\text{-}24\ hr}$ values of [redacted] and [redacted] respectively. This dose in the [redacted] was also associated with a drop in blood pressure (BP) and an increase in heart rate (HR) which was also reversible. These effects were mainly seen in the first [redacted] and as the terminal half-life was [redacted] is therefore associated with the peak plasma concentration (which at this dose [redacted] the MTD in the [redacted] is the equivalent to [redacted] in 60 kg human. Although the MTD was not reached in the GLP [redacted] study the free exposure level was [redacted] which was substantially lower than the free exposure seen in the [redacted] at MTD [redacted], however the onset of toxicity in a [redacted] non-GLP study in the [redacted] was associated with a free exposure of [redacted], and severity and number of animals affected increased with free exposure [redacted] therefore onset of toxicity is dependent on exposure and starting dose will be set based on MTD in the 28 day [redacted] study (see below).

The lowest doses producing efficacy were [redacted] (regression [redacted]) in [redacted] xenograft study which was associated with a C_{max} and AUC of [redacted] and [redacted]. In [redacted] xenografts the lowest dose to produce efficacy [redacted] was [redacted] which was associated with AUC of [redacted] (free [redacted]) whereas [redacted] was associated with [redacted] regression and plasma concentration above [redacted] and [redacted] inhibition pMCM2 in the [redacted] (AUC not measured). The bioavailability in the [redacted] was only [redacted] in comparison to [redacted] in both the preclinical toxicity species, and the terminal half-life in the [redacted] is substantially shorter which may start to explain the higher doses required in [redacted] for efficacy. Therefore, the exposure at which toxicity occurs is [redacted] above the [redacted] exposure for robust Cdc7 inhibition.

The MTD in dogs was [redacted] which equates to a human equivalent dose of [redacted]. When this

is allometrically scaled for surface area (60 kg human) and with an assumed 6-fold safety margin; the starting dose has been set at 30 mg.

Table 5 Summary of Toxicity findings from non-clinical Toxicology studies

Finding	[redacted]				[redacted]			
	Effect Dose (mg/m²)	**Exposure** AUC µM •h, (Cmax µM)	**No Effect Dose (mg/m²)**	**Exposure** AUC µM •h, (Cmax µM	**Effect Dose (mg/m²)**	**Exposure** AUC µM •h, (Cmax µM	**No Effect Dose (mg/m²)**	**Exposure** AUC µM •h, (Cmax µM
Morbidity/Mortality	[redacted]							
Clinical Signs								
Cardiovascular								
Liver								
Kidney								
Ocular								
GI								

Finding	[redacted]				[redacted]			
	Effect Dose (mg/m^2)	**Exposure** AUC µM •h, (Cmax µM)	**No Effect Dose (mg/m^2)**	**Exposure** AUC µM •h, (Cmax µM	**Effect Dose (mg/m^2)**	**Exposure** AUC µM •h, (Cmax µM	**No Effect Dose (mg/m^2)**	**Exposure** AUC µM •h, (Cmax µM
Haemapoietic and Lymphatic System	[redacted]							
Reproductive	[redacted]							
Other	[redacted]							

[a]based on 14 day [redacted] repeat dosing; [b]based on 28 day [redacted] dosing study -GLP; [c]based on 5 day cardiovascular [redacted] repeat dosing study; [d] based on based on [redacted] repeat dosing study; [e] based on based on 28 day [redacted] repeat dosing study-GLP; [f] 4 day non GLP tox study; # [redacted] than the NOAEL in [redacted] 28 study. [redacted] * [redacted]; ϕ [redacted] for the duration of the study; N/S – toxicity was not seen in this species; NM- not measured; BUN serum urea nitrogen

2.4 Clinical experience (Other compounds in the same class)

No previous clinical studies have been conducted with LY3143921 hydrate. However, three Cdc7 inhibitors have entered Phase I clinical trials.

NMS 1116354/NMS-354

Nerviano Medical Sciences developed a first in class group of Cdc7 kinase inhibitors. The lead compound PHA-767491 (NMS 1116354/NMS-354) is a nanomolar potency, ATP-competitive, small molecule Cdc7/Cdk9 inhibitor which produced apoptotic cell death in several cancer cell lines and inhibiting tumour growth in preclinical AML, colon and breast xenograft models but preserved cell viability in drug-treated normal human dermal fibroblasts [37, 38]. PHA-767491 was explored in phase I studies in solid and haematological malignancies (NCT01016327 and NCT01092052). Overall, a total of 39 patients were planned to be enrolled in two Phase I trials, but the trials were terminated as it was not possible to achieve sufficient drug exposure due to rapid metabolism and generation of a toxic metabolite. The dose limiting toxicities have not yet been disclosed for this trial.

BMS-863233/XL413

In collaboration with Exelixis, Bristol Myer Squibb (BMS) introduced a Cdc7 inhibitor (BMS-863233/XL413) into the clinic with Phase I trials in patients with refractory haematological malignancies (NCT00838890) and with advanced and/or metastatic solid tumours (NCT00886782). Development BMS-63233/XL413 was terminated due to an unfavourable pharmacological profile observed in Phase 1 clinical evaluation (Exelixis, Inc quarterly SEC filing).

TAK-931

In February 2016 Takeda Pharmaceutical opened a Phase I, dose-escalation study (NCT02699749) to evaluate the safety, tolerability, and pharmacokinetics of a Cdc7 inhibitor, TAK-931, in adult patients with advanced non haematologic tumours in Japan. Patients will receive TAK-931 capsule at a dose of 30 mg orally once on days 1 to 14 of a 21 day cycle. A total of 40 subjects were planned to be enrolled in this study. This study has now completed.

At the start of the clinical trial, the information referenced from the latest Investigator Brochure was current. Updates to the Investigator Brochure will not be reflected in this section so please refer to the most current version of the Investigator Brochure for up to date information.

2.4.1 Expected safety profile for LY3143921 hydrate

Based on preclinical experience with LY3143921 hydrate, potential toxicities associated with LY3143921 hydrate administration could include the following:

Hepatic changes

Reversible minimal to moderate [redacted] and [redacted] was seen in some animals at doses [redacted] equivalent to [redacted] in 60 kg human. [redacted] was also seen in [redacted] of [redacted]. Therefore at human equivalent dose of ≥[redacted] there may be some liver toxicity.

Liver function tests will be undertaken as part of the clinical programme.

LY3143921 hydrate was found to be a competitive inhibitor of [redacted] therefore it unlikely that there will be a drug-drug interaction (DDI) at clinical exposures however patients taking co-medications metabolised through CYP2C19, 2C9 and/or CYP3A4 will be carefully monitored.

Blood pressure

A dose dependent [redacted] was seen over the [redacted] in [redacted] ≥[redacted] accompanied by a [redacted] and a [redacted] which were all reversible. This is thought to result from peripheral vasodilatation. Therefore, at human equivalent dose of [redacted] hypotension and mild tachycardia may be a side effect.

Supine and standing blood pressure will be monitored hourly for the first 6 hours after the first dose of LY3143921 hydrate in all patients and every 4 hours thereafter up to 24 hours. Patients will also be asked to measure their supine and standing blood pressure twice daily at home during their first cycle of treatment.

Ocular changes

Minimal [redacted] was observed in animals dosed at [redacted] for the initial 4 days followed by [redacted] thereafter. This effect was not seen in the recovery phase. Slight to moderate [redacted] was not frequent but observed in [redacted] out of [redacted] at [redacted] and [redacted] out of [redacted] at [redacted] Therefore, at human equivalent dose of [redacted] there may be some ocular changes.

Ophthalmological findings were evident during the preclinical safety programme and could potentially occur in the last cohort of dose escalation. Ophthalmological examination of the eye will be undertaken during screening and where warranted based on clinical symptoms, during routine clinical examinations.

Renal changes

[redacted] in the [redacted] was noted in one month GLP toxicology dose study in [redacted] administered [redacted] (of 3), and one female at [redacted] (of 3) HED [redacted], no other histopathology was noted and these changes were not seen in the recovery phase. [redacted] was also seen in [redacted] at ≥[redacted] equivalent to [redacted] in 60 kg human no renal changes were seen in the GLP [redacted] study in [redacted] with the highest dose tested [redacted]. At higher does [redacted] in the non GLP study the [redacted] correlated with in [redacted] and [redacted]. Therefore, renal dysfunction maybe a possible side effect of LY3143921 hydrate administration at human doses ≥[redacted]

Standard Phase I kidney function tests will be undertaken as part of the clinical programme.

Gastrointestinal changes

Overt [redacted] was not seen in the [redacted] GLP study [redacted] study but there was evidence of [redacted] in the [redacted] at the [redacted] which was absent by the end of the recovery period. In non GLP studies [redacted] was [redacted]. Therefore, GI toxicity might be an attribute of treatment with LY3143921 hydrate at doses at above the MTD. Potentially doses of [redacted] may produce [redacted]

Standard Phase I laboratory evaluations will be undertaken, as well as symptom directed physical examination. Patients will be evaluated at study visits for any adverse events relating to the GI tract. Further investigations or imaging may be initiated if clinically indicated.

Haematological changes

Reversible minimal to mild [redacted] was present in the [redacted] in the [redacted] GLP study in one animal, [redacted] and in two animals at the MTD [redacted] and these effects were reversible. At doses above the MTD [redacted] and [redacted] were also observed. Onset of [redacted] and [redacted] was ≥[redacted] in the non GLP [redacted] study. This increased in severity with dose and was not seen in either of the GLP studies in [redacted] and [redacted]. Haematopoietic system toxicity potentially could present at [redacted]; it is not uncommon in agents that affect the cell cycle and is clinically manageable.

Standard Phase I haematological evaluations will be undertaken as part of the clinical programme

Reproductive organ changes

[redacted] toxicity and [redacted] in the [redacted] were seen at all doses in the one month toxicity study in the [redacted] furthermore in the seven day pilot study [redacted] were observed at all dose levels tested [redacted] Reproductive changes may be a possible side effect of administration of LY3143921 hydrate from the starting dose.

Patients will be warned of potential impact of the IMP on fertility and standard clinical trial contraceptive practices will be required.

Please refer to the current IB for up to date information on toxicities reported during this clinical trial.

2.5 Rationale for the trial

The aim of this trial is to evaluate LY3143921 hydrate, a Cdc7 inhibitor in patients with advanced solid tumours, for tolerability and safety, to establish the recommended Phase II dose/schedule and investigate potential predictive and pharmacodynamic biomarkers of drug activity.

The target population is adult patients with advanced solid tumours for whom there is no standard treatment option, for whom standard care options are of limited utility or those refractory to standard therapies.

The study will enrich for those patients with tumours most likely to receive benefit. Our hypothesis is that cancers with p53 loss-of-function mutational status may be particularly sensitive to inhibition of Cdc7. Therefore, the study expansion phase will focus on mCRC (Cohort 1) and squamous NSCLC (Cohort 2), both of which have high levels of p53 mutation and functional loss. Additionally a third cohort (Cohort 3) enriched for other tumours of interest with reported high levels of p53 loss or mutation including high grade serous ovarian carcinoma (HGSOC), squamous carcinoma of the oesophagus, squamous carcinoma of the head and neck (Human Papilloma Virus [HPV] negative), urothelial cancer, triple negative breast cancer and pancreatic cancer and exploring an intermittent dosing schedule will be enrolled.

3 TRIAL DESIGN

3.1 Clinical trial objectives and endpoints

3.1.1 Primary objectives and endpoints

Table 6: Trial Objectives and Endpoints

Primary Objectives	Endpoints
To propose a RP2D by determining the MTD and schedule of LY3143921 hydrate	Determining the maximal dose at which no more than one patient out of up to six patients at the same dose level experience a highly probably or probably drug related DLT and determining the schedule of administration at which the MTD is established
To assess the safety and toxicity profile of LY3143921 hydrate	Determining causality of each AE to LY3143921 hydrate and grading severity according to NCI -CTCAE Version 4.02

3.1.2 Secondary objectives and endpoints

Secondary Objectives	Endpoints
To determine the PK profile of LY3143921	Determine the C_{max}, T_{max}, area under the curve (AUC), plasma half-life, volume of distribution and clearance of LY3143921
To assess the efficacy of LY3143921 hydrate	Determine the response rate, median progression free survival of patients treated with LY3143921 hydrate according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1

3.1.3 Tertiary objectives and endpoints

Tertiary Objectives	Endpoints
To retrospectively investigate [redacted] that can be associated with [redacted] to LY3143921 hydrate	Assessment of [redacted] in pre treatment tumour samples
To determine the relationship between [redacted] tissue	Assessment of markers including but not limited to [redacted] expression and [redacted] samples
To explore [redacted] levels in [redacted] to LY3143921 hydrate	Assessment of [redacted] following treatment and use including but not limited to, [redacted]

3.2 Design of the clinical trial

This is a multi-centre, first-in-human, Phase I, open label dose escalation and expansion trial, in patients with incurable advanced/metastatic solid tumours.

It is expected that between 40 and 115 patients will be required to complete this trial, the final number depending on the number of dose levels explored.

LY3143921 hydrate will be administered orally. LY3243921 hydrate will initially be administered once or twice daily. Alternative dosing frequencies may be considered by the Sponsor based on emerging toxicity and PK data during the study (See Section 5.2). A single dose will be administered 7 days prior to Cycle 1 Day 1, on Cycle 1 Day -7 (dose escalation phase only); from Cycle 1 Day 1 each cycle of treatment will consist of 21 days continuous dosing. Patients may continue initially for up to 12 cycles. The patient may continue beyond 12 cycles in accordance with section 5.7. The starting dose will be 30 mg.

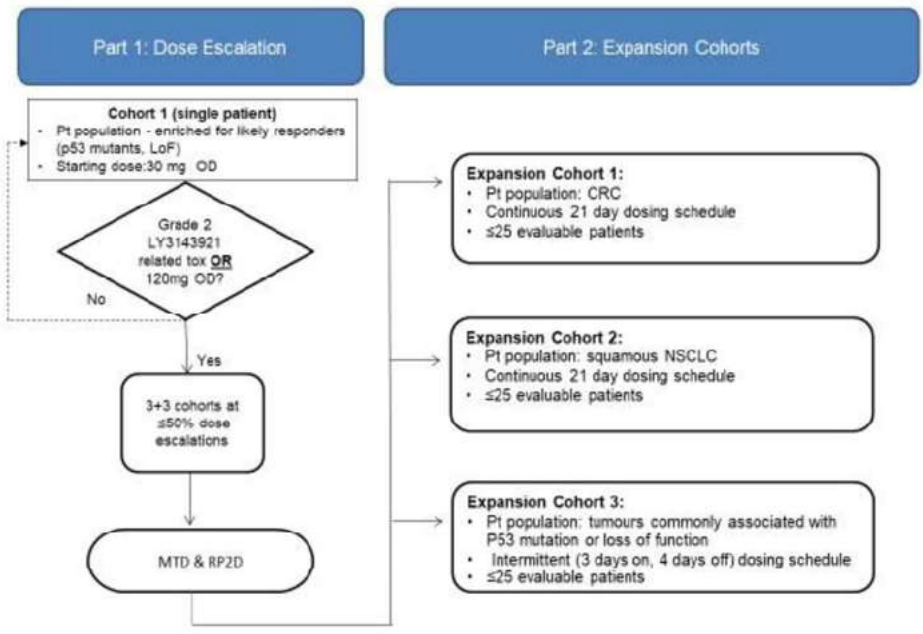
The trial will consist of two parts (see Figure 4):

- Part 1 - dose escalation phase. An accelerated trial design will be used in the dose escalation with single patient cohorts being explored at the lowest dose levels to restrict the number of patients exposed to possible sub-therapeutic doses, but will change to 3 to 6 patient cohorts once probably or highly probably LY3143921 hydrate related National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade 2 toxicities are seen, or earlier if agreed at dose escalation cohort review committee discussions.

- Part 2 – an expansion phase of three cohorts is planned at the recommended Phase II dose (RP2D) with up to 25 patients in each cohort as follows: Cohort 1: patients with colorectal carcinoma (CRC) administered LY3143921 hydrate on a continuous 21 day dosing schedule; Cohort 2: patients with squamous non-small cell lung cancer (NSCLC) administered LY3143921 hydrate on a continuous 21 day dosing schedule and Cohort 3: patients with solid tumours enriched for tumours commonly associated with P53 mutation or loss of function administered LY3143921 hydrate on an intermittent, 3 days on, 4 days off per week (21 day cycle) dosing schedule.

  It is expected that a minimum of six patients in Cohorts 1 and 3 will have pre and post treatment tumour and skin biopsies and a minimum of six patients in Cohort 2 will have pre and post treatment skin biopsies (See Section 7.2 for details).

Figure 4: Study Design Schema



3.3 Definition of dose limiting toxicity

Some of the dose limiting toxicity (DLT) and maximum tolerated dose (MTD) definitions are derived from the NCI-CTCAE Version 4.02. Please note that not all of the events described as DLTs are fully supported by NCI-CTCAE but are formed by amalgams of different events in order to assist with assessments of adverse events.

A DLT is defined as **a highly probably or probably drug-related AE occurring during the first cycle** (28 days including the single dose of LY3143921 hydrate on Cycle 1 Day -7) during the dose escalation phase. However, all significant toxicities will be considered in dose review decisions and the determination of the Phase II dose. A DLT must fulfil one or more of the following criteria:

- neutropenia Grade 4 (absolute neutrophil count [ANC] < 0.5 x 10^9/L) for ≥ five days *see note
- febrile neutropenia (ANC <1.0 x 10^9/L) and either a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38.0°C (100.4°F) for more than one hour)
- infection (documented clinically or microbiologically) with Grade 3 or 4 neutropenia (ANC <1.0 x 10^9/L)
- thrombocytopenia Grade 4:
  - a) for ≥ five days *see note, or
  - b) associated with active bleeding, or
  - c) requiring platelet transfusion.
- Grade 3 or 4 hypotension (requiring sustained therapy for ≥24hours)
- Fatal event.
- Grade 3 or 4 toxicity to organs other than the bone marrow. This includes Grade 3 and 4 biochemical AEs as DLTs
  EXCLUDING:
  - Grade 3 nausea in patients who have not received optimal treatment with anti-emetics
  - Grade 3 or 4 vomiting in patients who have not received optimal treatment with anti-emetics; or
  - Grade 3 or 4 diarrhoea in patients who have not received optimal treatment with anti-diarrhoeals
  - Alopecia
  - Transient (< 7 days), asymptomatic Grade 3 biochemical abnormalities if agreed by the Centre for Drug Development (CDD) and the Study Team, including the CI

Any other related toxicity preventing administration of more than 25% of planned doses of IMP during Cycle 1 may also be considered a DLT.

*Note: In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia, a full blood count must be performed at least on Day 5 after the onset of the event to determine if a DLT has occurred. The investigator must continue to monitor the patient closely until resolution to Grade 3 or less.

Should any change be made to the grade or causality of an AE during the trial that may alter its DLT status, the CDD must be informed immediately as this may affect dose escalation decisions.

3.4 Definition of maximum tolerated dose

The maximum tolerated dose (MTD) will be determined as the dose level below that at which two out of up to six patients at the same dose level experience a DLT as defined in Section 3.3.

The maximum administered dose (MAD) could also equal the MTD in the event that dose escalation is stopped before two DLTs are observed at a given dose level due to the expectation that higher dose levels would be too toxic to administer to patients.

The recommended dose for the expansion phase will be determined following discussion of the MTD, all clinically relevant toxicity, efficacy data, PK and available pharmacodynamic data by the Sponsor, CI and Principal Investigators (PIs).

3.5 Patient evaluability

3.5.1 Safety

All patients who meet the eligibility criteria and receive at least one administration of LY3143921 hydrate will be evaluable for safety review.

3.5.2 Response

All patients who meet the eligibility criteria, receive at least 75% of the planned doses of LY3143921 hydrate in the first two cycles and have a baseline assessment of disease will be evaluable for response.

To be assigned a status of stable disease (SD), follow-up measurements must have met the SD criteria at least once and at least six weeks after the initial dose of LY3143921 hydrate is given. There is no requirement for repeat assessments to be performed in order for the patient to be assigned a status of complete response (CR) or partial response (PR).

3.5.3 Dose Escalation

In the single patient dose escalation phase of this study, the patient must have received their planned doses of LY3143921 hydrate during the first cycle (28 day DLT period) before a decision is made to dose escalate. Once the dose escalation cohorts are expanded, patients must have received ≥75% of their planned dose of LY3143921 hydrate during the first cycle (28 day DLT period) in order to dose escalate. If any patients in the three to six patient cohorts receive <75% of their planned doses during the first cycle (28 day DLT period) for reasons other than LY3143921 hydrate related toxicity, further evaluable patients may need to be recruited before a decision can be made (see section 5.7.1).

4 PATIENT SELECTION

4.1 Eligibility criteria

The patient must fulfil the eligibility criteria (listed in Sections 4.1.1 and 4.1.2).

4.1.1 Inclusion criteria

1. Written (signed and dated) informed consent and be capable of co-operating with treatment and follow-up.
2. Histologically proven advanced or metastatic solid tumours, refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient.

   For Phase Ia (dose escalation): Enriched for patients with tumours commonly associated with p53 mutation or loss of function:

   a. Colorectal cancer (CRC)
   b. High grade serous ovarian cancer (HGSOC)
   c. Non small-cell lung cancer (NSCLC, squamous cell variant)
   d. Squamous carcinoma of the oesophagus
   e. Squamous carcinoma of the head and neck (HPV negative)
   f. Urothelial cancer
   g. Breast cancer (triple negative type)
   h. Pancreatic cancer

   For Phase Ib (expansion cohorts): Cohort 1: patients with metastatic CRC; Cohort 2: patients with squamous NSCLC and Cohort 3: patients with solid tumours commonly associated with p53 mutation or loss of function (as described above for the Phase 1a part of the trial).

   - Consent for pre-treatment and post-treatment fresh tumour biopsy samples in a minimum of six patients in expansion Cohorts 1 and 3, optional for all other patients.
   - Consent for pre and post treatment skin punch biopsy in a minimum of six patients in each expansion cohort, optional for all other patients.
3. Life expectancy of at least 12 weeks.
4. World Health Organisation (WHO) performance status of 0 or 1.
5. Haematological and biochemical indices within the ranges shown below:

Laboratory Test	Value required
Haemoglobin (Hb)	≥9.0 g/dL / 90g/L *(no prior transfusion within last 4 weeks) or ≥10.0 g/dL / 100g/L (transfusion within last 4 weeks)*
Absolute neutrophil count (ANC)	≥1.5 x 10^9/L
Platelet count	≥100 x 10^9/L
Serum bilirubin	≤1.5 x upper limit of normal (ULN)
Alanine amino-transferase (ALT) and aspartate amino-transferase (AST)	≤ 2.5 x (ULN) (or ≤5 x ULN in the presence of liver metastases)
Calculated creatinine clearance (using the Wright or Cockcroft &Gault [C&G] formula)	≥ 50 mL/min
PT and aPTT	≤1.5 x ULN Therapeutic INR values between 2.0 and 3.0 are acceptable for patients taking warfarin or other oral anticoagulants.
Albumin	≥ 80% of the lower limit of normal

6. Age 18 years or over.

7. Consent must be given for use of archived tumour samples.
8. Disease must be either evaluable or measurable using RECIST v1.1 criteria.

4.1.2 Exclusion criteria

1. Systemic anti-cancer therapy (with the exception of life-long hormone suppression such as luteinising hormone-releasing hormone (LHRH) agents in prostate cancer) or another investigational agent during the previous 4 weeks (6 weeks for nitrosureas, Mitomycin-C) is not permitted. Previous use of radiotherapy is permitted except where there has been a large volume of bone marrow irradiated or where the irradiated lesion is the only one suitable for RECIST measurability.
2. Ongoing toxic manifestations of previous treatments (Grade 2 or greater according to NCI-CTCAE v4.02) with the exception of alopecia or certain Grade 2 toxicities, which in the opinion of the investigator and Sponsor should not exclude the patient – these should be discussed on a case by case basis.
3. Symptomatic brain metastases or spinal cord compression.
4. Significant baseline hypotension (<90 mmHg systolic or <50 mmHg diastolic) or symptomatic hypotension at any level of BP.
5. Uncontrolled hypertension (>160 mmHg systolic or >100 mmHg diastolic in a relaxed, temperate setting with patient quiet and seated with their arm outstretched and supported) *should the patient present with BP >160 mmgHg/90 mmHg at screening see appendix 4.
6. Patients with a known left ventricular ejection fraction (LVEF) <50%. An echocardiogram (ECHO) must be performed in all patients.
7. Women of child-bearing potential[3] (or are already pregnant or lactating). However, those patients who meet the following points are considered eligible:
    - Have a negative serum or urine pregnancy test before enrolment and;
    - Agree to use two forms of contraception (one effective form plus a barrier method) [oral, injected or implanted hormonal contraception and condom; intra-uterine device and condom; diaphragm with spermicidal gel and condom] or agree to sexual abstinence[4], effective from the first administration of LY3143921 hydrate, throughout the trial and for six months afterwards.
8. Male patients with partners of child-bearing potential. However, those patients who meet the following points are considered eligible:
    - Agree to take measures not to father children by using a barrier method of contraception [condom plus spermicide] or to sexual abstinence[4] effective from the first administration of LY3143921 hydrate, throughout the trial and for six months afterwards.
    - Men with partners of child-bearing potential must also be willing to ensure that their partner uses an effective method of contraception for the same duration for example, hormonal contraception, intra-uterine device, diaphragm with spermicidal gel or sexual abstinence.
    - Men with pregnant or lactating partners must be advised to use barrier method contraception (for example, condom plus spermicidal gel) to prevent exposure of the foetus or neonate.

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[3] A woman is considered of childbearing potential i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

[4] Abstinence is only considered to be an acceptable method of contraception when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

9. No major surgery within 4 weeks prior to the patient receiving Cycle 1 Day-7 (for dose escalation) or C1 Day1 (for dose expansion). If minor surgery has been performed within 2 weeks of the start of trial treatment then patients must have recovered, and the sponsor and CI should be notified of the nature of this and agree to patient inclusion.
10. At high medical risk because of non-malignant systemic disease including active uncontrolled infection.
11. Known to be serologically positive for Hepatitis B, Hepatitis C or Human Immunodeficiency Virus (HIV) (mandatory testing not required).
12. Significant cardiovascular disease as defined by:
    a. History of congestive heart failure requiring therapy (NYHA III or IV – Appendix 3)
    b. History of unstable angina pectoris or myocardial infarction up to 6 months prior to trial entry
    c. Presence of severe valvular heart disease
    d. Presence of a ventricular arrhythmia requiring treatment
13. Past history of corneal ulceration, dry eye syndrome, glaucoma. Contact lenses should also be avoided during participation in the trial.
14. Is a participant or plans to participate in another interventional clinical trial, whilst taking part in this Phase I study of LY3143921 hydrate. Participation in an observational trial or interventional clinical trial which does not involve administration of an IMP and which would not place an unacceptable burden on the patient in the opinion of the Investigator and Medical Advisor would be acceptable.
15. Any other condition which in the Investigator's opinion would not make the patient a good candidate for the clinical trial.

4.2 Patient enrolment

Before enrolling the patient in the trial, the Investigator or designated representative should determine the eligibility of the patient during the trial screening period. Please ensure that Cancer Research UK's (CRUK's) Centre for Drug Development (CDD) are notified of any eligibility concerns at least four working days before first dose is planned.

Eligible patients must be enrolled in the electronic data capture (EDC) system by site staff and then registered by the CDD before their first dose of LY3143921 hydrate is administered. Eligible patients will be allocated a study number by the EDC system during the enrolment process. The CDD will send confirmation of the patient registration, including the assigned dose level and schedule, to the investigator following enrolment of the patient. LY3143921 hydrate may only be administered after this confirmation has been received.

5 TREATMENT

5.1 Selection of the Phase I starting dose and schedule

The highest dose of LY3143921 hydrate tested in GLP studies which was [redacted] was deemed to be the MTD based on the drop in BP, increase in heart rate and moderate liver centrilobular necrosis. When allometrically scaled this gives the equivalent human dose [redacted] based on 60 kg person). Using a reasonable safety factor to reduce this dose to approximately one sixth, 30 mg dose given as [redacted] once daily has been set as the starting dose.

5.2 Dosing schedule/treatment schedule

During the dose escalation phase (Phase Ia) patients will receive a single, oral dose of LY3142921 hydrate as an in-patient on Cycle 1 Day -7 (timing of day -7 is flexible to accommodate public and bank holidays, but should be no more than 11 days or less than 6 days prior to Cycle 1 Day 1).

From Cycle 1 Day 1 LY3143921 hydrate will be administered orally once or twice daily on a 21 day schedule. Each cycle will consist of 21 days and patients may receive up to 12 cycles of LY3143921 hydrate. If the patient is showing benefit (as defined in section 5.7) they may continue beyond 12 cycles after discussions between and Sponsor and Chief Investigator. The starting dose will be 30 mg once daily.

Alternative dosing schedules may be explored in the dose expansion phase.

An accelerated trial design will be used with single patient cohorts being explored at the lowest dose levels to restrict the number of patients exposed to potentially sub-therapeutic doses, but will change to 3 to 6 patient cohorts once probably or highly probably LY3143921 hydrate related NCI-CTCAE Grade 2 or higher toxicities are seen, or on the advice of the dose escalation cohort review committee.

After cohorts are expanded to 3+3 patients, an additional cohort of 3 to 6 patients may be recruited and administered LY3143921 hydrate (at or below a dose level and schedule previously tested) in a fasted and a non-fasted manner to observe the impact of food on drug exposure. This scenario may be considered when, after discussions between Sponsor and Investigators, it is thought that allowing participants to eat may improve tolerability and ameliorate any symptoms due to fasting, for example persistent CTCAE Grade 2 nausea. In this additional cohort, a single oral dose of LY3143921 hydrate will be given on Day -7 (non-fasted) and a full PK profile up to 48 hours (h) obtained. Non-fasted means that patients may eat and drink as normal in the period prior to and after their dose. A set food intake will not be defined but on Day -7 the patient's food intake prior to dosing will be recorded and may be reviewed in conjunction with PK data. Subsequently, on Cycle 1 Day 1 patients should fast for 3 h before LY3143921 hydrate administration and for 2 h after administration and a PK profile up to 8-10 h post dose obtained. If the twice daily dosing schedule is being followed, patients will only be required to fast before and after their first dose; they will be allowed to eat and drink prior to their second dose. This will allow an intra-patient assessment of exposure in fasted/non-fasted states.

For all patients undergoing non-fasted/fasted assessment, Day -7 PK will be reported and reviewed by the Sponsor and Chief/Principal Investigator prior to Cycle 1 Day 1 administration. PK parameters (including AUC, C_{max}, $T_{1/2}$) will be reviewed and compared to those analysed thus far in fasted patients. Providing the non-fasted dosing is well tolerated and the PK profile is acceptable from a toxicity-exposure relationship in comparison to all available preclinical and clinical data then the patient will be allowed to eat for the remainder of Cycle 1 dosing following the fasting requirement on Cycle 1 Day 1 and continue to take LY3143921 hydrate for further cycles non-fasted.

Recruitment and review of clinical and PK data for this cohort will follow the same restrictions and requirements as all other cohorts. Intra-patient non-fasted and fasted PK data will be evaluated upon completion of the cohort at the point of dose review to determine the non-fasted/fasted effect on drug exposure and whether LY3143921 hydrate can be administered non-fasted in future patients. Providing LY3143921 hydrate is well tolerated and there are no exposure concerns when comparing

inter and intra-patient PK profiles, dose escalation will continue. In subsequent cohorts, patients would continue to be non-fasted on Day -7 and fasted for the first dose of Cycle 1 Day 1 as stated above to continuously monitor the effect of non-fasted drug administration with increased drug dose and to identify any changes to pharmacokinetics with increasing dose i.e. exposure plateau.

If after completion of this extra cohort of patients, it is determined that patients cannot receive LY3143921 hydrate in the non-fasted state (e.g. due to unfavourable PK) then patients will continue to be treated fasted using prophylactic antiemetics as appropriate (type and frequency as determined by the treating physician on an individual patient basis) with the aim of preventing and controlling any nausea and vomiting.

5.3 Communication Plan where dose escalation is to occur

5.3.1 Organisation and preparation for dose decision meetings.

Dose decision meetings will be organised by the Sponsor for review of patient data after each patient in the single patient dose escalation cohorts has completed their DLT period (28 days including Cycle 1 Day -7 dose). When the cohorts are expanded to 3+3, dose decision meetings will be organised by the Sponsor for review of patient data once each cohort is complete (see section 5.4.3 for further details).

The dose decision for treatment of subsequent patients will be based upon safety data from all patients in a cohort after the last patient in the existing cohort is evaluable for dose escalation decisions. Data from previous cohorts will also be taken into account in dose decision meetings.

Required attendees / functional groups are as defined in the Sponsor's SOP: Sponsor PV representative, Sponsor Medical Sciences representative (MS), Sponsor Clinical Study Manager or appropriate delegate, CI and PIs with patients at their sites undergoing review (a nominated sub- or co-investigator may attend in the PI's place if necessary). Optional attendees are Research Nurses or other relevant site staff and the following Sponsor representatives; Clinical Research Associates (CRAs), Clinical Study Co-ordinator (CSC), Clinical Data Manager (CDM) and, Project Leader (PL). PI's who do not have patients in the cohort under review are encouraged to attend but not required.

Prior to the dose decision meeting, the Sponsor will distribute the agenda and all necessary data to the meeting attendees and all study PIs if they are not available to attend the meeting, specifying which patients and data will form part of the review. The essential data to be reviewed to make decisions concerning changes in dose will be defined in the monitoring guidelines for the study. These will consist primarily of clinical data listings from Data Management (DM), safety data listings from Pharmacovigilance (PV) and required PK and pharmacodynamic assay data.

5.3.2 Areas to be discussed at dose decision meetings.

Areas which should be discussed at the dose decision meeting include:

- Outline any relevant criteria specified by the protocol relating to changes in dose levels to the attendees e.g. study dose escalation scheme, dose limiting toxicity (DLT) criteria, criteria for expansion of cohorts etc. Patients treated since the last dose review meeting including IMP related adverse events noted and duration of treatment.
- Assessment and agreement on any dose limiting toxicities that may have occurred and resulting actions.
- Relevant PK and/or PD data available since the last dose decision meeting including, where applicable, intra-patient non-fasted versus fasted PK profiles.
- Any additional relevant information relating to adverse events or patient safety which may have arisen following distribution of listings for the meeting and will therefore not be documented in the listings.
- Any possible concern after the review of cumulative data e.g. toxicities.
- Assessment and agreement on the appropriate next dose level or other action such as dose expansion, dose reduction or halt to recruitment.

5.3.3 Follow-up of dose decision meetings

Following the meeting the Sponsor will prepare and disseminate minutes documenting what data was reviewed for which patients and with the outcome stated. DLTs, SAEs discussed, medically important events (as specified by the protocol) and SUSARs will be documented fully in the minutes and listed by patient. If changes to these emerge as part of the review and discussion the minutes will reflect these and any actions to be taken as a result. Dose decision meeting minutes will be distributed by the Sponsor to the CI, all study PIs and any other relevant site staff.

If due to exceptional circumstances, the CI is not able to attend the dose review meeting, the meeting minutes will be sent to the CI by email who will respond to confirm agreement as soon as possible with the dose decision prior to recruitment of the next patient to the relevant cohort.

The outcome of the dose review will also be approved by the Sponsor's Head of Medical Sciences before recruitment of the next patient to the relevant cohort. Patients can only be registered and treated on the study following email confirmation from the Sponsor to the site of the agreed dose level and schedule for the specific patient and non-fasted versus fasted dosing requirements (if applicable).

5.3.4 Dissemination of Safety data between dose decision meetings

Safety information relating to SAEs and DLTs will be collected and provided to the MHRA and Ethics Committee as outlined in Section 9. Where the Sponsor becomes aware of significant relevant safety information (such as a DLT) during treatment of patients on the study, this will be communicated to all PIs and relevant site staff by email as soon as is reasonably possible. Updates regarding the DLT assessment and actions to be taken will also be provided by email where needed with follow-up phone-calls where required.

5.4 Dose escalation scheme

5.4.1 Single patient cohorts

Initial cohorts will consist of single patients until the emergence of any NCI-CTCAE v4.02 Grade 2 or higher toxicity that is probably or highly probably related to LY3143921 hydrate, when the cohort will be expanded to include three to six patients. Cohorts may also be expanded to three to six patients at an earlier time point following review of PK results which suggest that cohort expansion would be appropriate [redacted] concentrations of [redacted]), [redacted], corresponding with preclinical values where mild, reversible hypotension was observed in dogs). Subsequent cohorts will also be expanded to three to six patients. If a DLT is seen in the single patient cohort, up to six patients will be recruited. If one out of the six patients experiences a DLT, dose escalation will continue. Subsequent cohorts will expand to three to six patients.

5.4.2 Further dose escalation cohorts

If one out of three patients experiences a DLT (as defined in Section 3.3) up to six patients will be treated at that dose. If one out of up to six patients experiences a DLT, dose escalation will continue. If two or more out of up to six patients in a cohort experience a DLT, dose escalation will be stopped and this dose will be defined as the maximum administered (MAD). At least six patients will be treated at the dose level below the MAD or at an intermediate dose level in order to define the MTD. The MAD could also equal the MTD in the event that dose escalation is stopped before two DLTs are observed at a given dose level, due to the expectation that higher dose levels would be too toxic to administer to patients.

5.4.3 Dose escalation scheme

The clinical study team including the Chief Investigator (CI) will review all emerging data from patients already on study and receiving LY3143921 hydrate before determining the next dose level. The dose level of LY3143921 hydrate will be assigned according to the number of patients already enrolled at the current dose level, the number of DLTs (and any other drug related AEs) observed at the current dose level and the number of patients enrolled who are at risk of developing a DLT (see Section 3.3). Dose escalation review meetings will be held to determine if the dose level has been tolerated by the patients and if it is safe to escalate the dose and determine the next dose level. These reviews will be triggered when sufficient patients have had the opportunity to complete 1 cycle (28 days including the single dose on Cycle 1 Day -7). The safety data including a list of DLTs and all AEs will be reviewed along with all other required or available data.

Dose increases will initially be up to a maximum of 100% in single patient cohorts until a LY3143921 hydrate related NCI-CTCAE Grade 2 toxicity is seen or PK results suggest that cohort expansion would be appropriate ([redacted] of AUC [redacted] •h [redacted] •h and/or free C_{max} drug concentration of [redacted] After this point, subsequent cohorts will revert to a standard 3+3 format with dose escalation steps reduced to a maximum of 50%, driven by reported safety data and available PK data.

If the dosing frequency is switched from once to twice daily dosing, the total dose that the patients in the first increased frequency daily dosing cohort receive in one day will not exceed 33% more than the dose given to the previous cohort.

In the single patient cohorts the next patient can receive their first dose of LY3143921 hydrate once the preceding patient has completed their DLT period (28 days including the single dose on Cycle 1 Day-7) and the Sponsor and study team has deemed it safe to proceed to the next cohort.

When the cohorts are expanded to 3+3 format, the first patient entered in a cohort must have received their Cycle 1 Day-7 and at least Days 1 to 7 of Cycle 1 daily doses before the next patient can be entered. The second, third and any subsequent patients in a cohort may be entered in parallel.

Patients who receive less than 75% of their planned doses during the first cycle (28 day DLT period) for reasons other than toxicity will not be evaluable for assessment of DLT for dose review decisions and may be replaced in the cohort. Reported safety information for these patients may however be considered to guide the percentage change in dose levels. In order to make the decision to escalate the LY3143921 hydrate dose in the expanded 3+3 cohorts, at least 3 evaluable patients must have completed their DLT period.

5.4.4 Intra-patients dose escalations

No intra-patient dose escalation will be allowed.

5.5 Dose Expansion Phase

The dose expansion phase may be opened to recruitment following determination of the RP2D. If an adverse event occurs that is deemed to represent a significant issue with tolerability or safety during the dose expansion phase at the RP2D, the dose level and/or schedule for new patients in an Expansion Cohort may be reduced or modified based on the ongoing safety reporting. Any decision to change the dose level or schedule will be discussed and agreed by the Sponsor, CI and PIs and communicated to all participating sites.

5.6 Dose and scheduling modifications

5.6.1 Dose schedule change and dose reductions

Patients who experience an NCI-CTCAE Grade 3 or 4 LY3143921 hydrate related (possibly, probably or highly) toxicity (or any other grade of event where the Sponsor or Principal investigator (PI) believes the patient would benefit from a schedule or dose change [except Grade 4 abnormal liver function

tests as described later in this section]) that goes on to resolve to Grade ≤ 1 or recover to baseline within 15 days may recommence treatment as follows:

1. Patients on a continuous dosing schedule may recommence on an intermittent schedule of 3 days on treatment followed by 4 days off treatment every week.

2. Patients enrolled on an intermittent schedule (either patients whom have switched to an intermittent schedule or patients whom commenced on study on an intermittent schedule) may receive a reduced dose of 270 mg BD (i.e. the dose level below the MTD defined in the dose escalation phase of the trial).

If the AE has not resolved or recovered to baseline within 15 days the patient will be taken off-study. If the patient experiences the same or a different DLT again at the reduced dose, one further dose reduction may be permitted with approval from the Sponsor and CI.

The first incidence of Grade 4 toxicity with regard to the management of abnormal liver function tests requires that the patients discontinue study treatment immediately and that follow up continues (measurement of liver enzymes) until resolution of abnormal liver function tests. No re-challenges are permitted in this case.

5.6.2 Dose delays

In the event of an NCI-CTCAE Grade 3 or 4 LY3143921 hydrate related (possibly, probably or highly) toxicity (or any other grade where the PI believes the patient would benefit from a break in taking study medication, except Grade 4 abnormal liver function tests as described in section 5.6.1), dosing of LY3143921 hydrate should be delayed up to 14 days until these toxicities have resolved to Grade ≤1 or returned to baseline. If there is no recovery after a 14 days delay, the patient should be withdrawn from the trial.

In the event of non-IMP related events, necessitating a dose delay, a maximum delay of 21 days is permitted.

At the start of each cycle, if haematology and biochemistry results do not fall within the ranges specified below treatment should be delayed until the ranges are met, and for a maximum of 14 days, unless otherwise approved by the CDD and Chief Investigator. If there is no recovery after a 14 day delay, the patient should be withdrawn from the trial.

Laboratory Test	Value required
Haemoglobin (Hb)	≥8.0 g/dL / 80g/L *(no prior transfusion within last 3 weeks) or ≥10.0 g/dL / 100g/L (transfusion within last 3 weeks)*
Absolute neutrophil count (ANC)	≥1.0 x 10^9/L
Platelet count	≥75 x 10^9/L
Serum bilirubin	≤1.5 x upper limit of normal (ULN)
Alanine amino-transferase (ALT) and aspartate amino-transferase (AST)	≤ 2.5 x (ULN) (or ≤5 x ULN in the presence of liver metastases)
Calculated creatinine clearance (using the Wright or Cockcroft & Gault [C&G] formula)	≥ 50 mL/min
PT and aPTT	N/A not repeated after screening
Albumin	≥ 25 g/dL

5.7 Duration of LY3143921 hydrate administration

LY3143921 hydrate administration should continue for up to 12 cycles unless (a) the patient asks to be withdrawn, (b) there is evidence of disease progression or (c) the patient is experiencing unacceptable toxicity or (d) the investigator feels the patient should be withdrawn for any other reason. Other reasons are listed in Section 11.

If the Sponsor and CI agree that a patient is benefiting from LY3149321 hydrate (i.e. has stable or responding disease as measured by RECIST version 1.1 and the patient is not experiencing any intolerable effects from LY3143921 hydrate then the patient and their PI can choose to continue with treatment beyond 12 cycles. The Sponsor will review a full toxicity and efficacy profile including radiological data to confirm the reported objective response for that patient when considering the request. Following the PI confirming their agreement that continuing with IMP is in the patient's best interest, a review of the patient's clinical data and a risk benefit assessment will be performed by the Sponsor. Written confirmation of the patient's willingness to continue and understanding of the potential risks of continuing to receive LY3143921 hydrate beyond 70 cycles will be obtained by the PI at this review point. This review will be performed every 4-8 cycles as a minimum. The decision to allow further cycles of LY3143921 hydrate beyond 12 cycles will be at the discretion of the Sponsor and CI and dependent on IMP availability. If the Sponsor decides not to allow the patient to continue treatment based on the information provided or on other information received, then the Sponsor's decision is final.

5.7.1 Replacement of patients

Patients will be replaced by another patient at the same dose level during the dose escalation phase if less than 75% of planned doses of LY3143921 hydrate are administered during first cycle for reasons other than drug-related (possibly, probably or highly) toxicity.

Patients will be replaced in the expansion cohorts if less than 75% of planned doses of LY3143921 hydrate are administered during their first cycle for reasons other than drug-related (possibly, probably or highly) toxicity, unless there is evidence of progressive disease.

Replacement of patients will be confirmed by the Sponsor. There may be circumstances based on the emerging data from the trial which result in a patient not being replaced. This will be documented by the Sponsor.

5.8 Concomitant medication and treatment

Patients should be given appropriate anti-emetic(s) to take home with instructions to take if nausea develops.

Concomitant medication may be given as medically indicated, including vaccinations. Some vaccinations may be subject to specific Sponsor risk-assessment. Details (including name and start and stop dates of the concomitant medication) given must be recorded in the patient's medical records and details entered into the electronic case report form (eCRF).

Palliative radiotherapy may be given concomitantly for the control of bone pain or other symptoms. These irradiated lesions will not be evaluable for response. The patient must not receive other anti-cancer therapy or investigational drugs while on the trial.

Patients receiving anti-hypertensive treatment should be closely monitored and withdrawal of these treatments should be considered if there is any evidence of hypotension.

6 PHARMACEUTICAL INFORMATION

6.1 Supply of LY3143921 hydrate

A complete certificate of analysis and Qualified Person (QP) certification must be provided with each batch of the investigational medicinal product (IMP) LY3143921 hydrate capsules.

For information on LY3143921 hydrate capsules and re-ordering of supplies, contact the Clinical Research Associate (CRA)/Clinical Study Manager (CSM) responsible for the trial who will arrange further supplies.

LY3143921 hydrate drug product will be supplied by:

Cancer Research UK Formulation Unit

[redacted]

Telephone Number: [redacted]

Email Address: [redacted]

The CRUK Formulation Unit must provide confirmation of the shipment to the CSM/CRA on dispatch of the IMP.

Capsules will be supplied in [redacted] containing [redacted] capsules per bottle.

The primary packaging for LY3143921 hydrate capsules will be labelled according to Eudralex Volume 4: Annex 13 'Investigational Medicinal Products' of the European Union guide to Good Manufacturing Practice (GMP).

Prior to dispatch of LY3143921 hydrate capsules to the clinical trial site a label detailing the investigator name and investigator site name will be added to the primary packaging at the MIA (IMP) licensed manufacturer in accordance with GMP. An example of the approved label can be found in the TMF and site Pharmacy File.

6.2 Pharmaceutical data

6.2.1 Formulation of LY3143921 hydrate

LY3143921 hydrate capsules will be supplied in [redacted] containing [redacted] of either [redacted] filled in [redacted]. The strength [redacted] and [redacted] relates to LY3143921 content and not LY3143921 hydrate content. The [redacted] strength will be in opaque [redacted] and [redacted] strength in [redacted].

6.2.2 Storage conditions

LY3143921 hydrate capsules must be stored at controlled ambient temperature in its original packaging in a secure, limited access storage area in the hospital pharmacy, protected from light.

6.2.3 Stability of LY3143921 hydrate capsules

Please refer to the label on the container (primary package) for the expiry date of the IMP.

6.2.4 Dispensing of LY3143921 hydrate capsules

Sufficient number of LY3143921 hydrate capsules must be dispensed on each occasion to cover the prescribed dose over the period to the next scheduled dispensing.

The LY3143921 hydrate capsules must not be removed from the original packaging or placed in any other container. On Cycle 1 Day -7 the required quantity of LY3143921 hydrate capsules to cover this single dose and the 21 days from Cycle 1 Day 1 should be dispensed; the single dose should be given to patients, then the original bottle(s) returned to pharmacy to be held separately from the unopened stock until Cycle 1 Day 1 when the remaining capsules should be given to the same patient.

When the bottles are dispensed, additional labelling must be applied according to local hospital policy which should not obscure the original manufacturer's label. The dispensed labels must have had prior approval from CRUK. Copies of the current CRUK approved dispensed labels will be held in the Pharmacy File together with the approved Annex 13 label.

Once a bottle has been opened the patient must be instructed to secure the cap fully between doses and store at room temperature and protected from light.

Patients must be instructed to ensure that LY3143921 hydrate capsules are kept out of sight and reach of children.

6.2.5 LY3143921 hydrate capsules administration

Before dispensing LY3143921 hydrate capsules, the exact dosage must always be double-checked by a second suitably qualified person. All checks and double-checks must be documented (signed and dated) and the documentation must be available for the CRA/CSM to verify.

The LY3143921 hydrate capsules must be swallowed whole (with water) and not chewed, crushed, dissolved or divided.

Patients will be provided with instructions as to which days they should take LY3143921 hydrate capsules. Patients on a continuous dosing schedule will take capsules daily for 21 days per cycle.

Patients on the intermittent dosing schedule will take LY3143921 hydrate capsules on Days 1-3, Days 8-10 and Days 15-17 of a 21 day cycle.

Patients are permitted to eat and drink as normal prior to dosing. Patients should aim to take the capsule(s) at the same time each day. Should a patient miss a scheduled dose in error, for example, forgetting to take the dose, then LY3143921 hydrate capsules may be administered up until 3 h after the scheduled dose. After this time the patient should wait until the next scheduled time before taking the dose. Should a patient miss a scheduled dose due to vomiting, the patient should not retake the dose and should wait until their next scheduled dose.

6.3 LY3143921 hydrate accountability

Accurate records of all IMP shipments, capsules dispensed and all IMP returned by patients must be maintained. This inventory record must be available for inspection at any time by CRAs or CSMs of the CDD. The IMP supplies are to be used only in accordance with this protocol and under the supervision of the Investigator.

Patients will be given the appropriate number of capsules to take with them to cover the number of planned doses until their next study visit. Patients will be asked to complete a study diary card to document drug administration and to bring any remaining capsules with them to each study visit. The Investigator should make every effort to ensure patients' compliance to treatment.

The Investigator undertakes not to destroy any unused or returned IMP unless authorised to do so by the CDD. Any unused IMP must be destroyed according to hospital procedures and properly accounted for using the IMP Destruction Form and also on the IMP Accountability Record. During the course of the trial the CRA will check the numbers of LY3143921 hydrate capsules shipped to the centre, the number used and the number destroyed or returned. The pharmacy will give an account of any discrepancy.

7 INVESTIGATIONS SCHEDULE

In cases where a patient has investigations at a different hospital, for example weekly blood samples, then it is the Investigator's responsibility to ensure he/she receives and reviews the reported results. These results must be available for source data verification (SDV). Laboratory reference ranges, including effective dates, and evidence of laboratory accreditation must be obtained from all laboratories used.

The Investigator or delegate must inform the CDD of any changes to the laboratory normal ranges or to any laboratory accreditation and provide any new documentation.

7.1 Pre-treatment evaluations

Details of all evaluations/investigations for enrolled patients, including relevant dates, required by the protocol must be recorded in the medical records.

Please also refer to the tabulated Schedule of Events in Section 7.5.

7.1.1 Obtaining written informed consent

Written informed consent must be obtained from the patient before any protocol-specific procedures are carried out.

The patient must be given adequate time to think about their commitment to the study. If more than 28 days has passed since informed consent was obtained before the start of LY3143921 hydrate dosing then the Investigator should consider whether repeat consent should be obtained from a patient. Should the informed consent document (ICD) have changed prior to the patient receiving their first dose of LY3143921 hydrate, the patient must be re-consented with the most up to date approved ICD.

Only the Principal Investigator (PI) and those Sub-Investigator(s) with delegated responsibility by the PI, and who have signed the Delegation Log, are permitted to obtain informed consent from patients and sign the consent form. All signatures must be obtained before the occurrence of any medical intervention required by the protocol (ICH GCP 4.8.8 and 8.3.1.2). The patient should sign and date the consent form in the presence of the PI/Sub-Investigator, who should then countersign the form after the patient. The date of the signatures of both the patient and the PI/Sub-Investigator obtaining informed consent should be the same.

The PI or the Sub-Investigator must inform the patient about the background to, and present knowledge of the normal management of their disease and LY3143921 hydrate and must also ensure that the patient is aware of the following points:

- That LY3143921 hydrate is new and that the exact degree of activity is at present unknown, but that treating him/her will contribute to further knowledge.
- The known toxicity of LY3143921 hydrate and the possibility of experiencing side-effects.
- The potential dangers of becoming pregnant (or the patient's partner becoming pregnant) and he/she has been given information about appropriate medically approved contraception (see Section 9.7).
- That he/she may refuse treatment either before or at any time during the trial and that refusal to participate will involve no penalty or loss of benefits to which they are otherwise entitled.
- Whom to contact for answers to pertinent questions about the research and their rights, and also who to contact in the event of a research-related injury.

A copy of the ICD must be given to the patient to keep and the original ICD must be filed in the Investigator Trial File (ITF) (unless otherwise agreed that the original document will be filed in the medical records and a copy kept in the ITF).

7.1.2 Evaluations within 28 days prior to the first administration of LY3143921 hydrate

(Cycle 1 Day -35 to Pre-dose on Cycle 1 Day -7 in dose escalation phase, or Cycle 1 Day -28 to Pre-dose on Cycle 1 Day 1 in dose expansion phase)

The following must be performed/obtained **within 28 days (+3 days) before** the patient receives their first dose of LY3143921 hydrate. Existing results such as radiological measurements may be used even where these investigations were performed prior to the patient's provision of informed consent for the study if they were performed within the required time window.

- Written informed consent (as detailed in Section 7.1.1) may be outside of this time frame;
- Demographic details;
- Medical history including prior diagnosis (histological or cytological), prior treatment, concomitant conditions/diseases and baseline signs and symptoms, concomitant treatment;
- Confirm availability and location of archival tumour specimen;
- Radiological disease assessments (+5 days): Radiological measurements (chest, abdomen and pelvis computerised tomography (CT) scan with oral and intravenous contrast) in accordance with Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1. If unable to receive IV contrast, then consider using non-contrast enhanced CT chest and MRI of abdomen and pelvis;
- Ophthalmological examination: slit lamp, visual acuity, visual fields (Humphrey 24-2 protocol), colour vision (Ishihara Colour plates), intraocular pressure (by Goldman Aplanation Tonometry), Optical Coherence Tomography/Scanning Laser Ophthalmoscopy both eyes (e.g. by the following or equivalent Heidelberg Spectralis: Multicolour SLO discs and maculae, Optic Nerve Fibre Layer Ring OCT ART100, Posterior Pole 64 line ART 30, cross hair single EDI cuts ART100), Fundus blue Autofluorescence and corneal OCT;
- Echocardiogram (ECHO);
- Dose-Expansion Only: Pre-treatment tumour biopsy **mandatory** for a minimum of six patients in expansion Cohorts 1 and 3. Optional for all other patients;
- Dose-Expansion Only: Pre-treatment skin punch biopsy for a minimum of six patients in each expansion cohort.

Note: Dependent on emerging pharmacodynamic data and recruitment to the expansion cohorts, the number of mandatory biopsies per cohort specified above and also the requirement for mandatory biopsies, may be revised by the Sponsor. This will be communicated to all Investigators.

Note that all adverse events (AEs), including serious adverse events (SAEs), must be monitored and recorded in the eCRF from the time the patient consents to any protocol-specific procedure (see Section 9 for further details).

7.1.3 Evaluations within 14 days prior to the first administration of LY3143921 hydrate

(Cycle 1 Day -21 to Pre-dose on Cycle 1 Day -7 in dose escalation phase, or Cycle 1 Day -14 to Pre-dose on Cycle 1 Day 1 in dose expansion phase)

The following must be performed within the **14 days (+2 days)** before the patient receives the first dose of LY3143921 hydrate:

- Female patients able to have children must have a negative result on a human chorionic gonadotropin (HCG) pregnancy test (serum or urine test is acceptable).

7.1.4 Evaluations within 7 days prior to the first administration of LY3143921 hydrate

(Cycle 1 Day -14 to Pre-dose on Cycle 1 Day -7 in dose escalation phase, or Cycle 1 Day -7 to Cycle 1 Day 1 in dose expansion phase)

The following must be performed **within 7 days (+1 day) before** the patient receives the first dose of LY3143921 hydrate:

- Complete physical examination;
- WHO performance status;
- Weight, temperature, blood pressure (BP, supine and standing) and pulse rate;
- Electrocardiogram (ECG);
- Laboratory tests (blood/urine samples) to confirm eligibility:

  Haematology – haemoglobin (Hb), red blood cells (RBC), white blood cells (WBC) with differential count (neutrophils and lymphocytes), and platelets;

  Biochemistry – sodium, potassium, adjusted calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST);

  Coagulation – PT and aPTT;

  Urinalysis – glucose, protein and blood.

  Enrolment of the patient on the study once eligibility has been confirmed (see Section 4.2).

7.2 Evaluations during the trial

7.2.1 Cycle 1 Day -7 (dose escalation phase only)

The timing of Cycle 1 Day -7 is flexible to accommodate public and bank holidays but should be no more than 11 days or less than 6 days before Cycle 1 Day 1 is scheduled.

Before LY3143921 hydrate administration:

- Symptom-directed physical examination: if clinically indicated;
- Food intake prior to dose to be recorded in patient records (if applicable);
- WHO performance status (if not performed in the preceding 24 hours);
- Weight, temperature, blood pressure (supine and standing) and pulse rate;
- Adverse events and concomitant medications: an assessment of any AE experienced since the previous visit must be made by the Investigator, Research Nurse or suitably qualified member of the Investigator's team. The start and stop dates of the AE together with the relationship of the event to the LY3143921 hydrate must be recorded in the medical records. All AEs must be graded according to NCI-CTCAE Version 4.02. (See Section 9 for further details regarding AE reporting requirements). Any concomitant treatment must be recorded in the medical records.
- Laboratory tests:
  - Haematology: detailed in Section 7.1.4.
  - Biochemistry: detailed in Section 7.1.4.

- Urinalysis: detailed in Section 7.1.4

- Research Samples: for PK, pharmacodynamic and genetic analysis. Please see Section 8.1 and Laboratory Manual for full details.

After LY3143921 hydrate administration:

- Hourly supine and standing BP measurements on the ward for the first 6 hours after dosing and then every 4 hours until 24 hours unless clinically indicated, in which case hourly BP measurements should continue until clinically stable. Note, blood pressure monitoring can be suspended over night while the patient is sleeping, unless ongoing monitoring is clinically indicated.
- Ophthalmological examination: if clinically indicated.

7.2.2 Cycle 1 Day 1 onwards

Visits may be conducted +/- 1 day of the schedule of events.

On the first day of each cycle **before** LY3143921 hydrate administration and weekly for the first 5 cycles (dose-escalation). In the dose expansion phase, visits may be reduced to once at the start of each cycle, with telephone contact replacing weekly visits until completion of the first 6 cycles. This will be dependent on emerging safety data and following discussions between Sponsor and CI:

- Symptom-directed physical examination: if clinically indicate

Ophthalmological examination: if clinically indicated

- WHO performance status (if not performed in the previous 24 hours)
- Weight, temperature, BP (supine and standing) and pulse rate
- Adverse events and concomitant medications: see section 7.2.1
- Laboratory tests:
  - Haematology: detailed in Section 7.1.4.
  - Biochemistry: detailed in Section 7.1.4.

  At a minimum, the assessments must be repeated before dosing on Day 1 of each cycle. Laboratory tests may be performed up to 24 hours prior to LY3143921 hydrate administration but results must be available and reviewed by the Investigator before LY3143921 hydrate is given. In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia a full blood count must be performed at least on Day 5 after the onset of the event to determine if a dose limiting toxicity has occurred. Continue close monitoring until resolution to Grade 3 or less.
  - Urinalysis on Day 1 of each cycle only: detailed in Section 7.1.4.

At the following time points only:

- Research Samples: Please see Section 8.1 and Laboratory Manual for full details.
- Cycle 1 Day 1 - hourly supine and standing BP measurements for the first 6 hours post-dose in all patients (applies to the first dose only for multiple daily dosing schedules). Thereafter for patients in the Escalation Phase Only: BP should then be measured every 4 hours unless clinically indicated until 24 hours after dosing. Note, blood pressure monitoring can be suspended over night while the patient is sleeping, unless ongoing monitoring is clinically indicated.
- Compliance: patients will be provided with a diary card and will be instructed to record when they take LY3143921 hydrate including details of any missed doses. The diary card should be

collected and checked for completeness and compliance in taking LY3143921 hydrate at each visit.

- Telephone assessment: Between Days 3-5 patients should be telephoned by a member of the Investigator's research team to assess for any emerging adverse events or tolerability concerns (Cycle 1 only).
- ECG: prior to the start of Cycles 2 and 3, then as clinically indicated
- Home BP monitoring: required daily during Cycle 1 with twice daily measurement of supine and standing BP, the first of which should be taken prior to LY3143921 hydrate administration and the second three to six hours after dosing (applies to *either* the morning or evening dose for twice daily dosing). Patients should be given detailed instructions on how to perform this at home and a diary card to record the measurements, which should be reviewed at each visit.
- Radiological disease assessments: to be performed at the end of Cycle 2 and every 2 cycles (+/- 5 days). Radiological measurements (chest, abdomen and pelvis computerised tomography (CT) scan with oral and intravenous contrast) in accordance with Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1. If unable to receive IV contrast, then consider using non-contrast enhanced CT chest and MRI of abdomen and pelvis. The frequency of radiological disease assessment may be reduced to every 3 cycles for any patient who is permitted to continue to receive LY3143921 hydrate beyond 12 cycles.
- Dose-Expansion Only: Post-treatment tumour Biopsy **mandatory** for a minimum of six patients in expansion Cohorts 1 and 3. A tumour biopsy for pharmacodynamic assessments will be taken during Cycle 2 after a minimum of 3 days continuous dosing. This is optional for all other patients.
- Dose-Expansion Only: Post-treatment skin punch biopsy **mandatory** for a minimum of six patients in each expansion cohort. A skin punch biopsy for pharmacodynamic assessments will be taken during Cycle 2 after a minimum of 3 days continuous dosing. This is optional for all other patients.

Note: Dependent on emerging pharmacodynamic data and recruitment to the expansion cohorts, the number of mandatory biopsies per cohort specified above and also the requirement for mandatory biopsies, may be revised by the Sponsor. This will be communicated to all Investigators.

7.2.3 Evaluations post Cycle 70

The following investigations/assessments should be performed at a clinical visit (except when indicated otherwise below) a minimum of every 4 - 8 cycles with the interval selected at the discretion of the Investigator:

- Symptom-directed physical examination: if clinically indicated;
- WHO performance status;
- Weight, temperature, blood pressure (supine and standing) and pulse rate;
- Ophthalmological examination: if clinically indicated;
- Electrocardiogram (ECG): if clinically indicated:
- Adverse events (AE) and concomitant medications: an assessment of any AE experienced since the previous contact must be made by the Investigator, Research Nurse or suitably qualified member of the Investigator's team on a 4-6 weekly basis by telephone or at a clinic visit. The start and stop dates of the AE together with the relationship of the event to the LY3143921 hydrate must be recorded in the medical records.
  All AEs must be graded according to NCI-CTCAE Version 4.02. (See Section 9 for further details regarding AE reporting requirements). Any concomitant treatment must be recorded in the medical records.

- Compliance: the patient will be instructed to complete a diary card and record when they take LY3143921 hydrate including details of any missed doses. The diary card should be collected and checked for completeness and compliance in taking LY3143921 hydrate at each visit.
- Laboratory tests (unless performed within 7 days of visit):

  - Haematology – haemoglobin (Hb), red blood cells (RBC), white blood cells (WBC) with differential count (neutrophils and lymphocytes), and platelets;

  - Biochemistry – sodium, potassium, adjusted calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST);

  - Urinalysis – glucose, protein and blood.
- Radiological disease assessments: to be performed as a minimum at the end of every 8 cycles (+/- 14 days). Radiological measurements (chest, abdomen and pelvis CT scan with oral and intravenous contrast) in accordance with Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1. If unable to receive IV contrast, then consider using non-contrast enhanced CT chest and MRI of abdomen and pelvis.
- Regular telephone contact (every 4-6 weeks) will be made with the patient by the Investigator, Research Nurse or suitably qualified member of the Investigator's team to assess for any adverse events or tolerability concerns and record concomitant medications.
- A formal clinical review and risk benefit assessment performed by the Investigator with written confirmation of the patient's willingness and understanding of the potential risks in continuing to receive LY3143921 hydrate.

7.3 Evaluations at Off-Study visit

Evaluations at the 'Off-Study' visit must be performed within 28 +/-7 days after the last dose of LY3143921 hydrate has been taken. The following investigations should be performed:

- Symptom-directed physical examination as clinically indicated;
- WHO performance status;
- Weight, temperature, BP (supine and standing) and pulse rate;
- Laboratory tests:

  Haematology: detailed in Section 7.1.4;

  Biochemistry: detailed in Section 7.1.4;

  Urinalysis: detailed in Section 7.1.4;
- ECG;
- Radiological assessment of tumour disease, unless the patient has been shown to have progressive disease on a previous study scan or an assessment has been performed within the previous 28 days;
- Ophthalmological examination: if clinically indicated;
- Assessment of AEs (also see Section 7.4); and
- Review of concomitant medications;
- Review of compliance upon collection of patient diary card.

7.4 Follow-up

7.4.1 Safety follow-Up

Any drug-related AEs still ongoing after the Off-Study visit will be followed up monthly until resolution to baseline or stabilisation, unless the patient starts another anti-cancer treatment.

Should an Investigator become aware of any drug-related SAEs after this period, these must also be reported to the CDD within the expedited timelines in Section 9.4.

7.4.2 Efficacy and survival follow-up

For patients who come off the trial for reasons other than progressive disease, every effort must be made by the site trial team to follow the patient at least 3 monthly +/- 2 weeks (through routine clinic appointments, NHS/HSC electronic data records or by phone calls if appropriate) to determine when progressive disease occurs. If the patient is lost to follow-up or has not progressed or died at the time of the interim database lock for patients receiving ≤ 70 cycles or the final database lock in the case of > 70 cycles being received (in order for the interim clinical study report and final clinical study report, respectively being produced), then the information will be censored as not known to have progressed/died at that time.

7.5 Schedule of events

7.5.1 Dose Escalation Phase

Observation/ Investigation	Screening			Cycle 1				Cycle 2 onwards	Off study	Follow-up
	Within 28 days (Day -35 to Pre-dose Day -7)	Within 14 days (Day -21 to Day -7)	Within 7 days (Day -14 to Pre-dose Day -7)	Day -7 (a)	Day 1	Day 8	Day 15	Day 1 and weekly until the end of cycle 5	Within 28 days after last dose of IMP	At least 3 monthly (j)
Archival Tumour Tissue	X									
Written informed consent	X									
Demographics	X									
Medical history	X									
Adverse event evaluation	From date of informed consent			Continually review					X	X (at least monthly)
Concomitant treatments	From date of informed consent			Continually review					X	
Radiological disease assessment	X (+5 days)							X (every 2 cycles only +/- 5 days)(b)	X (b)	
Pregnancy test (c)		X (if applicable)								
Ophthalmological examination (d)	X			X (as clinically indicated)					X (as clinically indicated)	
ECHO	X									
Physical examination (e)			X	X (as clinically indicated)					X (as clinically indicated)	
Temperature, supine and standing BP, pulse rate			X	X	X	X	X	X	X	
Weight			X	X	X	X	X	X	X	
WHO performance status			X	X	X	X	X	X	X	
Bloods for haematology and biochemistry (f)			X	X	X	X	X	X	X	
Blood for coagulation			X							
Urine sample for urinalysis			X	X	X			X (day 1 only)	X	
Electrocardiogram (ECG)			X					X (g)	X	
Blood pressure monitoring on ward (h)				X	X					

Observation/ Investigation	Screening			Cycle 1				Cycle 2 onwards	Off study	Follow-up
	Within 28 days (Day -35 to Pre-dose Day -7)	Within 14 days (Day -21 to Day -7)	Within 7 days (Day -14 to Pre-dose Day -7)	Day -7 (a)	Day 1	Day 8	Day 15	Day 1 and weekly until the end of cycle 5	Within 28 days after last dose of IMP	At least 3 monthly (j)
Home blood pressure monitoring (i)					X (daily)	X (daily)	X (daily)			
LY3143921 hydrate administration				X	X (daily)	X (daily)	X (daily)	X (daily)		
Compliance assessment				X	X	X	X	X	X	
Blood for PK analysis				X (refer to Lab Manual for exact timings)						
[redacted]				X						
Progression free survival										X

(a) Timing of Day -7 is flexible to accommodate public and bank holidays, but should be no more than 11 days or less than 6 days prior to Cycle 1 Day 1.
(b) **Radiological disease assessment**: Frequency may be reduced to every 3 cycles if a patient continues to receive LY3143921 hydrate beyond 12 cycles. Off Study visit assessment only needs to be performed if not performed within previous 28 days and/or if no PD seen on previous study scan.
(c) **Pregnancy test**: For female patients of child-bearing potential.
(d) **Ophthalmological examination** to be performed Pre-study then all subsequent examinations can be symptom-directed and only performed as clinically indicated.
(e) Complete **physical examination** to be performed Pre-study then all subsequent examinations can be symptom-directed and only performed as clinically indicated.
(f) **Clinical laboratory assessments**: should be performed within 7 days of Cycle 1 day -7 and weekly from Cycle 1 Day 1 for the first 5 cycles. After 5 cycles, the frequency of haematology and biochemistry assessments may decrease at the discretion of PI and Sponsor. At a minimum, the assessments must be repeated before dosing on Day 1 of each cycle. Laboratory tests may be performed up to 24 hours prior to LY3143921 hydrate administration but results must be available and reviewed by the Investigator before LY3143921 hydrate is given. In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia a full blood count must be performed at least on Day 5 after the onset of the event to determine if a dose limiting toxicity has occurred. Continue close monitoring until resolution to Grade 3 or less.
(g) **ECG;** to be performed prior to the start of cycles 2 and 3, then as clinically indicated.
(h) **Blood pressure monitoring as an in-patient:** Hourly supine and standing BP measurements on the ward for the first 6 hours after dosing and then every 4 hours thereafter unless clinically indicated until 24 hours after dosing on Cycle 1 Day -7 and Cycle 1 Day 1. Note, BP monitoring can be suspended overnight whilst the patient is sleeping, unless ongoing monitoring is clinically indicated.
(i) **Home blood pressure monitoring**: required daily during cycle 1 with twice daily measurement of supine and standing BP, the first of which should be taken prior to LY3143921 hydrate administration and the second three to six hours after dosing (applies to *either* the morning or evening dose for twice daily dosing).
(j) Monthly follow-up required ONLY for those adverse events and SAEs considered drug related (highly probably, probable or possible) and present off-study. Monthly follow-up for AEs to continue until resolution, return to baseline, stabilisation or patient starts another anti-cancer treatment. Information on disease status will also be captured 3 monthly for any patients who have not shown progressive disease at the time of their off-study visit.

7.5.2 Dose Expansion Phase

Observation/ Investigation	Screening			Cycle 1			Cycle 2 onwards	Off-Study	Follow-up
	Within 28 days (Day -28 to Pre-dose Day 1)	Within 14 days (Day -14 to Day 1)	Within 7 days (Day -7 to Pre-dose Cycle 1 Day 1)	Day 1	Day 8	Day 15	Day 1 and weekly until the end of Cycle 2 (m)	Within 28 days after last dose of IMP	At least 3 monthly (k)
Archival Tumour Tissue	X								
Written informed consent	X								
Demographics	X								
Medical history	X								
Adverse event evaluation	From date of informed consent			Continually review (l)				X	X (at least monthly)
Concomitant treatments	From date of informed consent			Continually review				X	
Radiological disease assessment	X (+5 days)						Every 2 cycles (+/- 5 days) (a)	X (a)	
Pregnancy test (b)		X (if applicable)							
Ophthalmological examination (c)	X			X (as clinically indicated)				X (as clinically indicated)	
ECHO	X								
Physical examination (d)			X	X (as clinically indicated)				X (as clinically indicated)	
Temperature, blood pressure and pulse rate			X	X	X	X	X	X	
Weight			X	X	X	X	X	X	
WHO performance status			X	X	X	X	X	X	
Bloods for haematology and biochemistry (e)			X	X	X	X	X	X	
Blood for coagulation			X						
Urine sample for urinalysis			X	X			X (day 1 only)	X	
Electrocardiogram (ECG)			X				X (f)	X	
Blood pressure monitoring on the ward (g)				X					
Home blood pressure monitoring (h)				X (daily)	X (daily)	X (daily)			
LY3143921 hydrate administration (n)				X	X	X	X		
Compliance assessment				X	X	X	X	X	
Tumour biopsy (i)	X						X		
Skin punch biopsy (i)	X						X		
Blood for PK analysis (j)				X (refer to Lab Manual for exact timings)					

Observation/ Investigation	Screening			Cycle 1			Cycle 2 onwards	Off-Study	Follow-up
	Within 28 days (Day -28 to Pre-dose Day 1)	Within 14 days (Day -14 to Day 1)	Within 7 days (Day -7 to Pre-dose Cycle 1 Day 1)	Day 1	Day 8	Day 15	Day 1 and weekly until the end of Cycle 2 (m)	Within 28 days after last dose of IMP	At least 3 monthly (k)
Blood for [redacted] (j)				X (refer to Lab Manual for exact timings)					
Blood for [redacted]				X					
Progression free survival									X

(a) **Radiological disease assessment**: Frequency may be reduced to every 3 cycles if a patient continues to receive LY3143921 hydrate beyond 12 cycles. Off-Study visit assessment only needs to be performed if not performed within previous 28 days and/or if no PD seen on previous study scan.
(b) **Pregnancy test**: For female patients of child-bearing potential.
(c) **Ophthalmological examination** to be performed Pre-study then all subsequent examinations can be symptom-directed and only performed as clinically indicated.
(d) Complete **physical examination** to be performed Pre-study then all subsequent examinations can be symptom-directed and only performed as clinically indicated.
(e) **Clinical laboratory assessments** should be performed within 7 days of Cycle 1 day 1 and weekly from Cycle 1 Day 1 for the first 2 cycles. After 2 cycles, the frequency of haematology and biochemistry assessments may decrease at the discretion of PI and Sponsor. At a minimum, the assessments must be repeated before dosing on Day 1 of each cycle. Laboratory tests may be performed up to 24 hours prior to LY3143921 hydrate administration but results must be available and reviewed by the Investigator before LY3143921 hydrate is given. In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia a full blood count must be performed at least on Day 5 after the onset of the event to determine if a dose limiting toxicity has occurred. Continue close monitoring until resolution to Grade 3 or less.
(f) **ECG;** to be performed prior to the start of cycles 2 and 3, then as clinically indicated.
(g) Ward **blood pressure monitoring:** Hourly supine and standing BP measurements on the ward for the first 6 hours after dosing.
(h) **Home blood pressure monitoring:** required daily during cycle 1 with twice daily measurement of supine and standing BP, the first of which should be taken prior to LY3143921 hydrate administration and the second three to six hours after dosing (applies to *either* the morning or evening dose for twice daily dosing).
(i) **Tumour and skin punch biopsy** to be collected within 28 days (+ 3 days) of the start of study treatment and then again during Cycle 2. The post treatment biopsies should be taken after a minimum of 3 days of continuous dosing. Tumour biopsies are mandatory in a minimum of 6 patients in expansion Cohorts 1 and 3. Skin punch biopsies are mandatory in a minimum of six patients in each expansion cohort.
(j) **Blood for PK[redacted] – please refer to Laboratory Manual for exact timings**
(k) Monthly follow-up required ONLY for those adverse events and SAEs considered drug related (highly probably, probable or possible) and present off-study. Monthly follow-up for AEs to continue until resolution, return to baseline, stabilisation or patient starts another anti-cancer treatment. Information on disease status will also be captured 3 monthly for any patients who have not shown progressive disease at the time of their off-study visit.
(l) Telephone assessment to be performed between Days 3-5 (Cycle 1 only) to assess any emerging adverse events and identify any tolerability issues.
(m) In the dose expansion phase, visits may be reduced to once at the start of each cycle, with telephone contact replacing weekly visits until completion of the first 6 cycles. This will be dependent on emerging safety data and following discussions between Sponsor and CI.
(n) Patients enrolled in Cohorts 1 and 2 will receive LY3143921 hydrate daily on a continuous 21 days schedule. Patients in Cohort 3 will receive LY3143921 hydrate on an intermittent schedule of 3 days on, 4 days off per week repeated in a 21 day cycle.

7.5.3 Post Cycle 70

Observation/ Investigation	Cycle 70 onwards			Off study	Follow-up
	Every 4-6 weeks (telephone or clinic visit)	Every 4-8 cycles (+/- 14 days) (clinic visit)	Every 8 cycles (+/- 14 days)	Within 28 days after last dose of IMP	
Formal assessment of suitability to continue on trial		X (a)			
Informed consent to continue extended treatment		X (a)			
Adverse event evaluation	X (continual assessment			X	X (at least monthly) (d)
Concomitant treatments	X (continual assessment)			X	
Radiological disease assessment			X	X (b)	
Ophthalmological examination		X (as clinically indicated)		X (as clinically indicated)	
Electrocardiogram (ECG)		X (as clinically indicated)		X (as clinically indicated)	
Physical examination		X (as clinically indicated)		X (as clinically indicated)	
Temperature, supine and standing BP, pulse rate		X		X	
Weight		X		X	
WHO performance status		X		X	
Bloods for haematology and biochemistry		X (c)		X (c)	
Urine sample for urinalysis		X		X	
LY3413921 hydrate administration	X (daily)				
Compliance assessment		X		X	
Progression free survival					X (at least 3 monthly) (d)

(a) **Formal assessment including consent to continue on trial**: performed at the same clinical visit every 4-8 cycles as a minimum.
(b) **Radiological disease assessment**: Off-Study visit assessment only needs to be performed if not performed within previous 28 days and/or if no PD seen on previous study scan.

(c) **Clinical laboratory assessment:** In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia a full blood count must be performed at least on Day 5 after the onset of the event. Continue close monitoring until resolution to Grade 3 or less.

(d) **Follow up:** Monthly follow-up required ONLY for those adverse events and SAEs considered drug related (highly probably, probable or possible) and present off-study. Monthly follow-up for AEs to continue until resolution, return to baseline, stabilisation or patient starts another anti-cancer treatment. Information on disease status will also be captured 3 monthly for any patients who have not shown progressive disease at the time of their off-study visit. If the patient is lost to follow-up or has not progressed or died at the time of the final database lock then the information will be censored as not known to have progressed/died at that time.

8 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

Please refer to the LY3143921 hydrate Laboratory Manual for instructions of collection, handling and storage.

Sample collection schemes or imaging time points may be reconsidered during the study upon collection of more PK and/or pharmacodynamic data.

8.1 Summary of PK and Pharmacodynamic assessments

Biomarker	Technology	Purpose of assay/ Rationale	Type of sample	Patient group	Total volume per patient during study	Time points
SECONDARY ENDPOINTS						
Pharmacokinetics of LY3143921	LCMS	To determine the PK profile of LY3143921	Blood (plasma)	Refer to Laboratory Manual	≤105mL	Up to 21 time points from first dose of LY3143921 hydrate to Off-Study Visit - refer to Laboratory Manual for further details
TERTIARY ENDPOINTS*						
[redacted]						

* These will be prioritised. Not all tertiary endpoints may be analysed

8.2 Secondary assessments

8.2.1 LY3143921 pharmacokinetics

LY3143921 levels will be measured in plasma by liquid chromatography mass spectrometry (LCMS) according to agreed standard operating procedures (SOPs) and validated methods.

The plasma/concentration/time data will be analysed using non-compartmental methods. The PK parameters will be determined for LY3143921 to include the maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the plasma concentration time curve (AUC), terminal elimination half-life ($T_{1/2}$), volume of distribution and clearance.

Approximately 5mL of blood will be collected from patients at up to 21 time points. The approximate total volume of blood withdrawn from each patient will be a maximum of 105 mL. Depending on emerging data, PK sampling may be explored in the expansion phase but will not exceed the volumes and time points described.

8.3 Tertiary/research assessments

8.3.1 Tertiary assays [redacted]

[redacted]
according to agreed SOPs and validated methods.

Please refer to the Study Specific Laboratory Manual for further instructions on all tertiary assay sample collection, handling and storage.

8.3.2 Tertiary assays [redacted]

[redacted] to measure biomarkers [redacted].

Please refer to the Study Specific Laboratory Manual for further instructions on all tertiary assay sample collection, handling and storage.

Sample collection schemes or time points may be reconsidered during the study upon collection of more PK or Pharmacodynamic data.

[redacted] Tertiary assays [redacted]

[redacted] patients in the dose expansion [redacted]

[redacted] according to agreed SOPs and validated methods. [redacted].

Please refer to the Study Specific Laboratory Manual for further instructions on all tertiary assay sample collection, handling and storage.

9 ASSESSMENT OF SAFETY

9.1 Investigator Responsibilities

The investigator is responsible for monitoring the safety of patients who have enrolled in the trial and for accurately documenting and reporting information as described in the following sections.

9.1.1 Medical Cover

The Chief/Principal Investigator (CI/PI) is also responsible for ensuring patients have access to 24 hour advice and/or care. Patients will be provided with the necessary contact numbers for both normal working and out of hours care. A copy of the protocol must be made available out of hours to ward staff and clinicians on call so that the appropriate advice may be given to the patient, the patient's relative or other care giver (for example GP). The CI/PI must ensure that should the on call clinician or ward staff require more advice than is in this protocol, that they have access to the Investigator or delegated members of the Investigator's team who can answer any questions.

9.2 Adverse event definitions

9.2.1 Adverse event

An adverse event (AE) is any untoward, undesired or unplanned medical occurrence in a patient administered an investigational medicinal product (IMP), a comparator product or an approved drug.

An AE can be a sign, symptom, disease, and/or laboratory or physiological observation that may or may not be related to the IMP or comparator.

An AE includes but is not limited to those in the following list.

- A clinically significant worsening of a pre-existing condition. This includes conditions that may resolve completely and then become abnormal again.
- AEs occurring from an overdose of an IMP, whether accidental or intentional.
- AEs occurring from lack of efficacy of an IMP, for example, if the Investigator suspects that a drug batch is not efficacious or if the Investigator suspects that the IMP has contributed to disease progression.

9.2.2 Serious adverse events

A serious adverse event (SAE) is any AE, regardless of dose, causality or expectedness, that:

- results in death;
- is life-threatening, defined as an event when the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient
- requires in-patient hospitalisation *or* prolongs existing in-patient hospitalisation (some hospitalisations are exempt from SAE reporting – e.g. hospital admissions planned prior to the patient entering the trial; overnight stays for planned procedures such as blood transfusions (Section 9.4.1));
- results in persistent or significant incapacity or disability;
- is a congenital anomaly or birth defect;
- is any other medically important event.*

*A medically important event is defined as any event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalisation. The development of drug dependence or drug abuse would also be examples of important medical events.

For fatal SAEs, wherever possible report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term. When available the autopsy report will be provided to the Sponsor.

If during the course of the study, other medically important events are identified and there is a requirement to report specific events outside of the standard criteria, this will be communicated to site and the protocol will be updated to reflect this.

Any dose limiting toxicity (DLT) must be reported to the CDD Clinical Study Manager (CSM) and CRA within 24 hours of site staff becoming aware of the DLT. The CDD Pharmacovigilance Department must be copied into any initial email notification.

Other reportable events that must be treated as SAEs are listed below.

- Pregnancy exposure to the IMP. Any pregnancy occurring in a patient or a patient's partner during treatment with an IMP or occurring within six months of the last IMP administration, must be reported to the Pharmacovigilance Department in the same timelines as an SAE. These should be reported even if the patient is withdrawn from the trial.
- Overdose with or without an AE.
- Inadvertent or accidental exposure to an IMP with or without an AE, including for example, spillage of the IMP that contaminates staff.
- Any AE that could be related to the protocol procedures, and which could modify the conduct of the trial.

9.2.3 Suspected, unexpected, serious adverse reactions

A SUSAR is a suspected, unexpected, serious adverse reaction. All AEs and SAEs will be assessed by CDD for seriousness, causality and expectedness. The Pharmacovigilance Department will expedite all SUSARs to the relevant Competent Authority/Authorities and the relevant Ethics Committee(s) within the timelines specified in legislation (SI 2004/1031 as amended).

9.2.4 Determining adverse event causality

The relationship of an AE to the IMP is determined as follows.

Highly probable

- Starts within a time related to the IMP administration and
- No obvious alternative medical explanation.

Probable

- Starts within a time related to the IMP administration and
- Cannot be reasonably explained by known characteristics of the patient's clinical state.

Possible

- Starts within a time related to the IMP administration and
- A causal relationship between the IMP and the AE is at least a reasonable possibility.

Unlikely

- The time association or the patient's clinical state is such that the trial drug is not likely to have had an association with the observed effect.

Not related

- The AE is definitely not associated with the IMP administered.

Note: Drug-related refers to events assessed as possible, probable or highly probable.

The Investigator must endeavour to obtain sufficient information to determine the causality of the AE (i.e. IMP, other illness, progressive malignancy etc) and must provide his/her opinion of the causal relationship between each AE and IMP. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

The following guidance should be taken into account when assessing the causality of an AE:

- Previous experience with the IMP and whether the AE is known to have occurred with the IMP.
- Alternative explanations for the AE such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding effects.
- Timing of the events between administration of the IMP and the AE.
- IMP blood levels and evidence, if any, of overdose.
- De-challenge, that is, if the IMP was discontinued or the dosage reduced, what happened to the adverse reaction?
- Re-challenge, that is, what happened if the IMP was restarted after the AE had resolved?

9.2.5 Expectedness

Assessment of expectedness for LY3143921 hydrate will be made by the Pharmacovigilance Department against the current version of the Investigator Brochure (IB).

9.3 Collection of safety information

9.3.1 Screening failures

For patients who fail screening, SAEs must be reported to the Pharmacovigilance Department, CDD from the date of consent until the date the patient is confirmed as ineligible.

9.3.2 Eligible patients

For eligible patients, SAE and AE collection and monitoring will commence at the time the patient gives their written consent to participate in the trial by signing the main study consent form and will continue until 28 days after the last administration of LY3143921 hydrate or until the patient starts another anti-cancer therapy.

Should an Investigator become aware of any drug-related SAEs after this 28 day period, these must also be reported to the CDD within the expedited timelines in Section 9.4.

9.3.3 Follow-up of AEs and SAEs

Follow-up of AEs with a causality of possible, probable or highly probable will continue until the events resolve, stabilise or the patient starts another anti-cancer therapy.

The Pharmacovigilance Department will make requests for further information on SAEs to the trial site at regular intervals. Requested follow-up information should be reported to the Pharmacovigilance Department in a timely manner and as soon as possible after receipt of the follow-up request. For fatal or life-threatening cases, follow-up information must be reported to the Pharmacovigilance Department as soon as possible.

9.3.4 Other safety information of interest

We will also collect information on the following situations, whether they are associated with an AE or not:

- Overdose *(any dose above that specified in the protocol, not necessarily intentional)*

- Abuse or misuse
- Medication error *(any unintentional error in the dispensing or administration of an IMP)*
- Occupational exposure *(to a person other than the patient, for example spilling of IMP on hands of nurse or splashing in the eye)*

Any occurrences of these should be reported in the same manner as SAEs (Section 9.4).

9.4 Reporting of SAEs to the Pharmacovigilance Department, CDD

All SAEs, regardless of causality, must be reported to the Pharmacovigilance Department in an expedited manner.

SAEs should be documented on an SAE report form, using the completion guidelines provided.

The SAE report form should be e-mailed to Pharmacovigilance Department within 24 hours of site staff becoming aware of the SAE.

e-mail: [redacted]

Each episode of an SAE must be recorded on a separate SAE report form. The NCI-CTCAE Version 4.02 must be used to grade the severity of each SAE, and the worst grade recorded. If new or amended information on a previously reported SAE becomes available, the Investigator should report this to the Pharmacovigilance Department on a new SAE report form.

If the SAE has not been reported within the specified timeframes, a reason for lateness must be provided when sending the SAE report form to the Pharmacovigilance Department.

Should the Investigator become aware of any IMP-related SAEs after the patient goes "off-study", these must also be reported to the Pharmacovigilance Department within the timelines specified above.

9.4.1 Events exempt from being reported as SAEs to the Pharmacovigilance Department

Events specified in this section do not require reporting as SAEs in this trial, unless hospitalisation is prolonged for any reason and then an SAE form must be completed. The events must still be recorded in the appropriate section of the electronic case report form (eCRF).

Elective admissions – Elective admissions to hospital for procedures which were planned prior to entering the trial are not SAEs. Hospitalisation for administration of the IMP according to the trial protocol is also exempt from being reported as an SAE, unless the patient experiences an event during the admission which would normally qualify as an SAE. Overnight stays or day admissions for planned procedures such as a blood transfusion would not qualify as an SAE.

Death due to disease progression- Cases of death due to disease progression do not require SAE reporting, unless considered related to the IMP.

9.5 Recording of adverse events and serious adverse events in eCRFs

All AEs, including SAEs, must be recorded in the eCRF for eligible patients. All concomitant medications, including herbal medications and supplements must be recorded. Any therapy used to treat the event must be recorded. The eCRF will be reconciled with the safety database during and at the end of the trial. Therefore, the sites should ensure the data entered on the SAE report form and the data entered into the eCRF are consistent. The CDD Medical Advisor and the Investigator(s) will regularly review the safety data from both the safety and the clinical database.

9.6 Urgent safety measures

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) in order to protect the patient of a clinical trial against any immediate hazard to their health or safety. This includes procedures taken to protect patients from pandemics or infections that pose serious risk to human health.

USMs may be taken without prior authorisation from the competent authority.

The Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC) must be notified within three days of such measures being taken.

Should the site initiate a USM, the Investigator must inform the Sponsor immediately either by:

- email: [redacted] or
- telephone: [redacted]

The notification must include:

- the date of the USM;
- who took the decision; and
- why action was taken.

The Sponsor will then notify the MHRA and the REC within three calendar days of USM initiation.

9.7 Pregnancy

Female patients who become pregnant from the time of giving written informed consent to the Off-Study visit must be withdrawn from study treatment immediately.

The Investigator must make every effort to try and ensure that a clinical trial patient or a partner of a clinical trial patient does not become pregnant during the trial or for six months afterwards. This should be done as part of the consent process by explaining clearly to the patient the potential dangers of becoming pregnant and also providing each patient with information about appropriate medically approved contraception. Two forms of medically approved contraception should be used, such as:

- oral contraceptives and condom;
- intra-uterine device (IUD) and condom;
- diaphragms with spermicidal gel and condom.

Contraception should be effective before the patient is enrolled on the trial, throughout the trial and for six months after completing the trial.

It should be explained to the patient that if his partner is pregnant or breast-feeding when he is enrolled on the trial, the patient should use barrier method contraception (condom plus spermicidal gel) to prevent the unborn baby or the baby being exposed to the LY3143921 hydrate.

However, if a patient or a partner of a patient does become pregnant, the reporting procedures below must be followed.

Any pregnancy occurring in a patient or a patient's partner during treatment with an IMP or occurring within six months of last IMP administration must be reported to the Pharmacovigilance Department within 24 hours of the site staff becoming aware of it using a Pregnancy Report Form (provided in the ITF). It is the Investigator's responsibility to obtain consent for follow-up from the patient or patient's partner and the contact details for the patient's partner's General Practitioner. The Pharmacovigilance

Department will follow-up all pregnancies for the pregnancy outcome via the Investigator, using a Pregnancy Report Form.

The Investigator must ensure that all patients are aware at the start of a clinical trial of the importance of reporting all pregnancies (in themselves and their partners) that occur whilst being treated with the IMP and occurring up to six months after the last IMP administration. The Investigator should offer counselling to the patient and/or the partner, and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Investigator monitoring of the patient should continue until the conclusion of the pregnancy, if the patient or patient's partner has consented to this. Monitoring of the baby should continue until 12 months after birth, if the patient or patient's partner has consented to this.

10 ASSESSMENT OF EFFICACY

10.1 Measurement of disease

Disease must be measured according to the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria given in Appendix 2.

10.2 Timing and type of tumour assessments

A thorough clinical and radiological evaluation of malignancy, as judged appropriate by the Investigator, and in line with the protocol, must be performed before a patient receives their first dose of LY3143921 hydrate. The same methods that detect evaluable lesions at baseline must be used to follow these lesions throughout the trial. To ensure compatibility, the radiological assessments used to assess response must be performed using identical techniques. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumour effect of a treatment.

All radiological assessments must be performed within four weeks before starting treatment with LY3143921 hydrate. The interval between the last anti-cancer therapy and these measurements must be at least four weeks (28 days).

Stable disease criteria must be met at least once after study entry at a minimum interval of six weeks to be defined as stable disease (SD). There is no requirement for repeat assessments to be performed in order for the patient to be assigned a status of CR or PR.

Copies of the scans must be available for external independent review if requested by the CDD.

10.2.1 Baseline evaluations

These must include radiological measurements of lesions in the chest, liver and abdomen by CT scan and/or other radiological measurements as clinically indicated or clinical measurements as appropriate e.g. assessment of palpable lesions or measurement of tumour markers. The preferred radiological modality is CT scan of chest, abdomen and pelvis with oral and intravenous contrast. If unable to receive IV contrast, then consider using non-contrast enhanced CT chest and MRI of abdomen and pelvis. All areas of disease present must be documented (even if specific lesions are not going to be followed for response) and the measurements of all measurable lesions must be recorded clearly on the scan reports. Any non-measurable lesions must be stated as being present. For clinical measurements, documentation by colour photography including a ruler to estimate the size of the lesion is strongly recommended, as this aids external independent review of responses. (See Appendix 2 Section 1.2.1 of RECIST 1.1 criteria)

10.2.2 Evaluations during and at 'off-study'

Tumour assessments must be repeated at the end of Cycle 2 and then every 2 cycles (+/- 3 days) or more frequently, when clinically indicated. For patients receiving > 70 cycles of treatment tumour assessments will be reduced to a minimum of every 8 cycles (+/- 14 days). All lesions measured at baseline must be measured at every subsequent disease assessment, and recorded clearly on the scan reports. All non-measurable lesions noted at baseline must be noted on the scan report as present or absent.

All patients, who are removed from the trial for reasons other than progressive disease, must be re-evaluated at the time of treatment discontinuation, unless a tumour assessment was performed within the previous four weeks.

It is the responsibility of the Principal Investigator to ensure that the radiologists are aware of the requirement to follow-up and measure every target lesion mentioned at baseline and comment on the non-target lesions in accordance with RECIST 1.1 criteria.

10.3 Tumour response

All patients who meet the eligibility criteria and receive at least 75% of the planned doses of trial medication in the first two cycles and have a baseline and at least one post-baseline assessment of disease will be evaluable for response. Patients who develop clear evidence of progressive disease (PD) without a formal disease assessment will be considered non-responders. To be assigned a status of stable disease (SD), follow-up measurements must have met the SD criteria at least once and at least six weeks after the initial dose of the investigational medicinal product (IMP) LY3143921 hydrate is given.

Should rapid tumour progression occur before the completion of 21 days the patient will be classified as having early progression (EP).

Tumour response should be classified as "not evaluable" (NE), only when it is not possible to classify it under another response category, for example, when baseline and/or follow-up assessment is not performed or not performed appropriately.

Expert reviewers appointed by CDD may undertake an independent review of the Investigator's assessed objective responses (CR and PR). The expert reviewers will include at least one specialist who is not an Investigator in the study. Any independent reviewer's assessment will also be documented in the final clinical study report (CSR) along with the assessment made by the Investigator. The eCRF will reflect the Investigator's opinion.

10.3.1 Recording of response in the eCRF

The applicable overall response category for each visit that includes disease assessment must be recorded in the eCRF.

10.3.2 Other definitions of outcome

Toxic death: Any death to which drug toxicity is thought to have a major contribution.

Early death: Death during the first 21 days of treatment.

11 PATIENT WITHDRAWAL BEFORE COMPLETION OF TREATMENT SCHEDULE

The Investigator must make every reasonable effort to keep each patient on trial for the whole duration of the trial (i.e. until 28 ± 7 days after last LY3143921 hydrate administration). However, if the Investigator removes a patient from the trial or if the patient declines further participation, final 'Off-Study' assessments should be performed ideally before any subsequent therapeutic intervention. All the results of the evaluations and observations, together with a description of the reasons for withdrawal from the trial, must be recorded in the medical records and in the eCRF.

Patients who decide to withdraw or stop taking LY3143921 hydrate are free to do so without giving any reasons. The data from these patients will be kept and used for analysis as part of this trial. The patient will be followed-up as clinically indicated and any data pertinent to their participation in this clinical trial (e.g. follow-up of adverse event information) will continue to be monitored and recorded as trial data unless the patient specifically withdraws consent.

Patients who are removed from the trial due to adverse events (clinical or laboratory) will be treated and followed according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the eCRF and on the serious adverse event (SAE) report form where necessary.

The following are justifiable reasons for the Investigator to withdraw a patient from study treatment. Every effort will be made to complete safety follow-up activities unless consent to safety follow-up has been withdrawn by the patient

- Adverse event/serious adverse event (AE/SAE);
- Withdrawal of consent;
- Serious deviation from the trial protocol (including persistent patient attendance failure and persistent non-compliance);
- Sponsor's decision to terminate the trial;
- Withdrawal by the Investigator for clinical reasons not related to LY3143921 hydrate
- Evidence of disease progression;
- Pregnancy (for female patients during the study)

12 DEFINING THE END OF TRIAL

The 'end of trial' is defined as the date when the last patient has completed the 'off-study' visit or the final follow-up visit (whichever is the latter). The 'off-study' visit is scheduled to take place 28 +/-7 days after the last dose of LY3143921 hydrate.

It is the responsibility of the CDD to inform the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC) within 90 days of the 'end of the trial' that the trial has closed.

In cases of early termination of the trial (for example, due to toxicity) or a temporary halt by the CDD, the CDD will notify the MHRA and the REC within 15 days of the decision and a detailed, written explanation for the termination/halt will be given.

Recruitment will cease when:

- The drug is considered too toxic to continue treatment before the required number of patients have been recruited.
- The stated number of patients to be recruited has been reached.
- The stated objectives of the trial are achieved.

Regardless of the reason for termination, all data available for patients at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the trial, CDD and the Investigators must ensure that adequate consideration is given to the protection of the patient's interest.

13 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

The final analysis will be conducted after one of the following conditions is met:

- The trial is terminated early
- The end of trial as defined in Section 12 has been reached.

If any patient continues to receive LY3143921 hydrate beyond 70 cycles then an interim analysis will be conducted to review the data collected to date. A data cut-off will be agreed and data for all patients up to the cut-off date, including any ongoing patients, will be cleaned and finalised. An interim clinical study report will be produced (see Section 14.6) based upon these data. The final analysis will then follow as detailed above. All data presentation and analyses in the following sections will be applicable to both the interim and final analyses.

13.1 Presentation of data

Data will be presented in a descriptive fashion. Variables will be analysed to determine whether the criteria for the trial conduct are met. This will include a description of patients who did not meet all the eligibility criteria, an assessment of protocol deviations, IMP accountability and other data that impact on the general conduct of the trial.

Baseline characteristics will be summarised for all enrolled patients. Patients who died or withdrew before treatment started or did not complete the required safety observations will be described and evaluated separately.

Treatment administration will be described for all cycles. Dose administration, dose modifications or delays and the duration of therapy will be described.

13.2 Safety

Safety data will be collected from the date of written consent. Safety variables will be summarised by descriptive statistics. Laboratory variables will be described using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02.

Adverse events (AEs) will be reported for each dose level and presented as tables of frequency of AEs by body system and by worse severity grade observed. Tables should indicate related and unrelated events.

13.3 Pharmacokinetics

The plasma concentration/time data will be analysed using non-compartmental methods. The PK parameters to be determined for LY3143921 hydrate include the maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), the area under the plasma concentration time curve (AUC), terminal elimination half-life ($T_{1/2}$), and volume of distribution and clearance of LY3143921 hydrate.

13.4 Pharmacodynamics

[redacted] biomarkers in skin and tumour samples. [redacted] and any other relevant [redacted] that is identified during the course of this study. [redacted] will be optimised for each [redacted].

[redacted] will be retrospectively investigated [redacted]

[redacted] will be investigated as [redacted].

13.5 Anti-tumour activity

The trial will include two parts:

Part 1 will be a dose escalation study identifying the recommended dose for Part 2 of the study.

Part 2 will include an assessment of efficacy and safety. The Sponsor and CI will regularly review the emerging data on clinical benefit and safety (CR, PR and SD on imaging and improvements in disease-related symptoms) in all evaluable patients in the expansion cohorts in Part 2, and link this to any earlier efficacy and safety data seen in the dose escalation cohorts in Part 1, and to our correlative laboratory research programme.

14 ADMINISTRATION

This trial is conducted under a clinical trial authorisation (CTA) and approval from the Medicines and Healthcare products Regulatory Agency (MHRA) and the relevant Research Ethics Committee(s) will be obtained before the start of this trial. This trial is sponsored and monitored by the CRUK CDD. Applicable regulatory requirements are described in this section.

14.1 Protocol deviations and amendments

The protocol should be adhered to throughout the conduct of the study, if a situation arises where the conduct of the study may not be in line with the protocol, then site should contact the CDD to discuss this.

Amendments to the protocol may only be made with the approval of the CDD. A protocol amendment may be subject to review by the assigned Ethics Committee, HRA and the MHRA. Written documentation of the Ethics Committee and HRA (Health Research Authority) (and if appropriate the MHRA) 'favourable opinion' (i.e. approval) must be received before the amendment can be implemented and incorporated into the protocol if necessary.

14.2 Serious breach of GCP

A serious breach is a breach which is likely to effect to a significant degree: the safety or physical or mental integrity of the subjects of the trial, or the scientific value of the trial.

In order that the Sponsor can fulfil their obligations in terms of reporting serious breaches of GCP to the MHRA within seven calendar days of identification, site staff must inform the Sponsor of any unplanned deviations to the trial protocol (or GCP principles) as soon as possible after the deviation occurs to allow prompt evaluation by the Sponsor.

14.3 Completion of the electronic case report form (eCRF)

Electronic CRFs approved by the CDD will be used to collect the data. The Investigator is responsible for ensuring the accuracy, completeness, clarity and timeliness of the data reported in the eCRFs.

Only the Investigator and those personnel who have signed the Delegation Log provided by the CDD and have been authorised by the Investigator should enter or change data in the eCRFs. Authorised users will be included on a user list in order to be provided access to the eCRF. All protocol required investigations must be reported in the eCRF. The Investigators must retain all original reports, traces and images from these investigations for future reference.

The collection and processing of personal data from the patients enrolled in this clinical trial will be limited to those data that are necessary to investigate the efficacy, safety, quality and usefulness of the study drug used in this trial. The data must be collected and processed with adequate precautions to ensure patient confidentiality and compliance with applicable data privacy protection according to the applicable regulations. The data collected will comply with Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data.

Data will be entered directly into electronic screens by authorised site personnel. Amendments to eCRF data will be made directly to the system and the system audit trail will retain details of the original value(s), who made the change, a date and time, and a reason for the change.

Once an eCRF form has been entered by the site personnel, the data are cleaned using manual and automated checks. Queries will be issued electronically to the site. Authorised personnel must

answer the queries by making relevant amendments to data or providing a response. Answered queries will be closed or reissued as appropriate.

Once the patient is 'off study' and the eCRF has been fully completed, the Investigator must provide an electronic signature to authorise the complete subject casebook.

At the end of the trial all eCRFs are retained and archived by the CDD and a PDF copy provided to the Investigator who is responsible for archiving at site.

14.4 Trial performance, monitoring, auditing and inspection

Before the trial can be initiated, the prerequisites for conducting the trial must be clarified and the organisational preparations made with the trial centre. CDD must be informed immediately of any change in the personnel involved in the conduct of the trial.

During the trial the CDD Clinical Research Associate (CRA) will be responsible for monitoring data quality in accordance with CDD's standard operating procedures (SOPs). A strategic monitoring approach, including targeted source data verification, will be implemented where appropriate.

Before the study start, the Investigator will be advised of the anticipated frequency of the monitoring visits. The Investigator will receive reasonable notification before each monitoring visit.

It is the responsibility of the CRA to:

- review trial records and compare them with source documents;
- check PK and pharmacodynamic samples and storage;
- discuss the conduct of the trial and the emerging problems with the Investigator;
- check that the drug storage, dispensing and retrieval are reliable and appropriate; and
- verify that the available facilities remain acceptable.

At the end of the trial all unused LY3143921 hydrate supplied must be destroyed at site (only once authorised to do so by the CRA or CSM) or if authorised by CRUK, returned to the supplier.

It is the responsibility of the Sponsor to notify the REC of the 'end of the trial'. (See definition in Section 12).

During the course of the trial, the Quality Assurance Department of the CDD, or external auditors contracted by the CDD, may conduct an on-site audit visit (ICH Topic E6 (R1) Guideline for Good Clinical Practice Sections 1.6).

Principal Investigators conducting this trial will accept the potential for inspection by the MHRA.

14.5 Source document verification

Unless agreed in writing, all data collected in the eCRF must be verifiable by the source data. Therefore it is the Investigator's responsibility to ensure that both he/she and his/her study team records all relevant data in the medical records. The Investigator must allow the CRA direct access to relevant source documentation for verification of data entered into the eCRF, taking into account data protection regulations. Entries in the eCRF will be compared with patients' medical records and the verification will be recorded in the eCRF.

Some source data may exist only electronically and be entered, or loaded directly into the eCRF.

The patients' medical records, and other relevant data, may also be reviewed by appropriate qualified personnel independent from the CDD appointed to audit the trial, NHS Trust staff and by regulatory

authorities. Details will remain confidential and patients' names will not be recorded outside the hospital.

14.6 Clinical study report

At appropriate intervals, interim data listings will be prepared to give the Investigator the possibility to review the data and check the completeness of information collected. All clinical data will be presented at the end of the trial on final data listings and a clinical study report will be prepared based on complete final data for all patients.

If any patient continues to receive LY3143921 hydrate beyond 70 cycles with the remaining patients having completed off study evaluations (unless this has been confirmed as not possible) and finalised data, CDD will prepare an interim clinical study report based on the data listings obtained from an interim lock of the database. The data set included in this report will consist of final clinical data from the patients off study and final clinical data from any long term, ongoing patient up to the cut-off date used for the interim database lock. A final clinical study report will then be prepared at the end of the trial, which will report complete final clinical data for all patients. Both the final clinical study report and any interim clinical study report will be submitted to the Investigator(s) for review and confirmation they accurately represent the data collected.

Summary results from the final clinical study report and, if applicable, the interim clinical study report will be provided by the CDD to the MHRA, and the Research Ethics Committee. Summary results from the final clinical study report will be provided by the CDD to clinicaltrials.gov.

14.7 Record retention

During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable both the conduct of a clinical trial and the quality of the data produced to be evaluated and verified. These essential documents (as detailed in Chapter V of Volume 10 (Clinical Trials) of The Rules Governing Medicinal Products in the European Union based upon Section 8 of the ICH GCP Guidelines), including source documents such as scans, trial related documents and copies of the eCRFs, associated audit trail and serious adverse event (SAE) report forms, shall show whether the Investigator has complied with the principles and guidelines of Good Clinical Practice (GCP).

All essential documents required to be held by the Investigator must be stored in such a way that ensures that they are readily available, upon request, to the Regulatory Agency or Sponsor, for the minimum period required by national legislation or for longer if needed by CDD. Records must not be destroyed without prior written approval from CDD.

The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

14.8 Ethical considerations

Before starting the trial, the protocol and patient informed consent document(s) (ICD) must go through the CDD's external review process, and be approved by the Protocol and Safety Review Board (PSRB) and receive the favourable opinion of the assigned REC.

It is the Chief/Principal Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The Chief/Principal Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented.

The Sponsor and Chief/Principal Investigator must ensure that the trial is carried out in accordance with the GCP principles and requirements of the UK Clinical Trials regulations (SI 2004/1031 and SI 2006/1928 as amended), the ICH GCP guidelines and the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and all subsequent amendments including Oct 2013.

14.9 Indemnity

This trial is sponsored by CRUK and therefore injury to a patient caused by the compounds under trial will not carry with it the right to seek compensation from the pharmaceutical industry. Cancer Research UK will provide patients with compensation for adverse side effects, in accordance with the principles set out in the Association of the British Pharmaceutical Industry (ABPI) guidelines on compensation for medicine-induced injury.

14.10 Publication policy and press releases

Results of this trial must be submitted for publication. The CDD must be involved in reviewing all drafts of the manuscripts, abstracts, press releases and any other publications. Manuscripts must be submitted to the CDD at least 30 days in advance of being submitted for publication to allow time for the CDD to schedule a review and resolve any outstanding issues. Abstracts and press releases must be submitted to the CDD at least 14 days in advance of being released.

Authors must acknowledge that the trial was sponsored by and performed with the support of CDD. The CI should be the principal author and any Investigator recruiting ≥ 10% of patients should be listed as an author - in order of numbers of patients recruited.

The contribution of the CDD should be recognised by at least one member of staff being included as an author on the publication. The Formulation Unit (FU) have developed and manufactured LY3143921 hydrate and so a member of the FU staff should be included as an author.

14.11 Guidance for disruption to trial conduct

In the event of disruption to trial activities, as demonstrated during the COVID-19 pandemic, the Sponsor 'Trial Disruption' policy should be reviewed to flag trial activities which the study team should consider for adaptation during the event. A risk-based approach will be applied to each trial to inform trial conduct throughout the period in order to protect the health and well- being of existing and future trial participants and ensure compliance with current regulatory guidance.

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