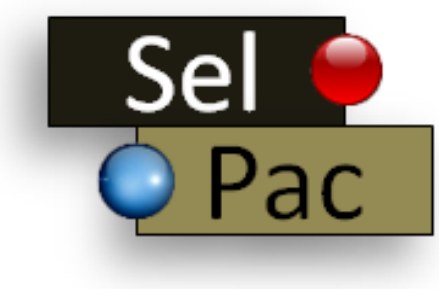


A Randomised three-arm, open label, Phase II study of continuous Selumetinib versus continuous or interrupted Selumetinib in combination with weekly Paclitaxel in Metastatic Uveal Melanoma

Study Sponsor:
University of Liverpool
Research Support Office
2nd Floor, Block D, Waterhouse Building
3 Brownlow Street
Liverpool
L69 3GL

EudraCT number:	2014-004437-22
ISRCTN number:	29621851
Sponsor protocol reference number:	UoL001077
Protocol version:	7
Date:	13-May-2020

LIVERPOOL CLINICAL TRIALS CENTRE LCTC

CANCER RESEARCH UK

Study Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Signature: See attached email approval confirmation **Date:** 29/06/2020

Dr Paul Nathan
Chief Investigator
Mount Vernon Cancer Centre
Mount Vernon Hospital
Middlesex
HA6 2RN

Signature: See attached email approval confirmation **Date:** 16/06/2020

Alexander Needham
Trial Statistician
Liverpool Clinical Trials Centre
University of Liverpool
1st Floor, Block C, Waterhouse Building
3 Brownlow Street
Liverpool
L69 3GL

Signature: See attached email approval confirmation **Date:** 18/06/2020

Mr Alex Astor
Head of Research Support Office – HLS
Research Support Office
University of Liverpool
2nd Floor, Block D, Waterhouse Building
3 Brownlow Street
Liverpool
L69 3GL

General Information

This document describes the SelPac trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Cancer Research UK Liverpool Clinical Trials Centre(LCTC)) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via LCTC.

Statement of Compliance

This study is designed to comply with the guideline developed by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and will be conducted in compliance with the protocol, LCTC Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004.

UK Registration

The SelPac study was opened in October 2015 prior to implementation of the HRA approval process in the UK. The trial underwent review and was approved by the National Research Ethics Service (NRES). Prior to March 2016 each centre that opened underwent a Site Specific Assessment by the relevant Trust Research and Development department and NHS sites were granted Research and Development Approval from their respective Trusts. Post March all new sites will undergo review via the HRA Approvals process to confirm for capacity and capability to deliver the study locally. In addition the study will hold a Clinical Trials Authorisation issued by the Medicines and Healthcare Products Regulatory Agency (MHRA).

Liverpool Clinical Trials Centre Merger

During the management of the SelPac Trial the Liverpool Cancer Trials Unit (LCTU) and the Clinical Trial Research Centre (CTRC) have merged to become the Liverpool Clinical Trials Centre (LCTC). The LCTC will continue to use the LCTC PORTAL as a legacy system for the duration of this trial, for the purposes of this protocol it will be referred to as the PORTAL only. For clarity, where SOPs or LCTC SOPs are referred to within this protocol a list of specific unit SOPs used for this trial has been compiled in document SelPac SOP Record.

Contact Details: Institutions

Sponsor:	Trial Management and Monitoring:	Translational Laboratory:
University of Liverpool Research Support Office 2nd Floor, Block D, Waterhouse Building 3 Brownlow Street Liverpool L69 3GL	**Liverpool Clinical Trials Centre** University of Liverpool 1st Floor, Block C Waterhouse Building 3 Brownlow Street Liverpool L69 3GL	**Liverpool GCP Facility** 1st Floor William Henry Duncan Building University of Liverpool 6 West Derby Street L7 8TX

Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:		Medical Expert who will Advise on Protocol Related Clinical Queries (If other than CI):
Chief Investigator: **Dr Paul Nathan** Mount Vernon Cancer Centre Mount Vernon Hospital Rickmansworth Road Northwood Middlesex HA6 2RN Tel: +44 (0) 1923 844966 Fax:+44 (0) 1923 844840	**LCTC Director: Carrol Gamble/** **LCTC Cancer Lead: Charlotte Rawcliffe** Liverpool Clinical Trials Centre University of Liverpool 1st Floor, Block C Waterhouse Building 3 Brownlow Street Liverpool L69 3GL	**Dr Joseph Sacco** The Clatterbridge Cancer Centre NHS Foundation Trust Clatterbridge Road Bebington Wirral CH63 4JY Tel: +44 (0) 151 334 1155 Fax: +44 (0) 151 482 7673 Email: joesacco@liv.ac.uk

Contact Details: Individuals

Medical Expert who will Evaluate SAE Reports (If other than CI):	Medical Expert who will Evaluate SAE Reports (If other than CI):	Medical Expert who will Evaluate SAE Reports (If other than CI):
Dr Pippa Corrie Oncology Centre (Box 193) Addenbrooke's Hospital Hill's Road Cambridge CB2 0QQ Tel: +44 (0) 1223 274 376 Fax:+44 (0) 1223 217 094 Email: pippa.corrie@addenbrookes.nhs.uk	**Dr Joseph Sacco** The Clatterbridge Cancer Centre NHS Foundation Trust Clatterbridge Road Bebington Wirral CH63 4JY Tel: +44 (0) 151 334 1155 Fax: +44 (0) 151 482 7673 Email: joesacco@liv.ac.uk	**Dr Ernie Marshall** The Clatterbridge Cancer Centre NHS Foundation Trust Clatterbridge Road Bebington Wirral CH63 4JY Tel: +44 (0) 151 334 1155 Fax: +44 (0) 151 782 7673 Email: EMarshall@NHS.Net

Medical Expert who will Evaluate SAE Reports (If other than CI):	Medical Expert who will Evaluate SAE Reports (If other than CI):
Dr Ruth Board Rosemere Cancer Centre Royal Preston Hospital Sharoe Green Lane Fulwood Preston PR2 9HT Tel: +44 (0) 1772 522916 Email: ruth.board@lthtr.nhs.uk	**Professor John Wagstaff** South West Wales Cancer Institute & Swansea College of Medicine Singleton Hospital Sketty Lane Swansea SA2 8QA Tel: +44 (0) 1792 285318 Email: john.wagstaff@swansea.ac.uk

Trial Coordinator:	Trial Statistician:	Data Manager:
Louise Handley Liverpool Clinical Trials Centre University of Liverpool 1st Floor, Block C Waterhouse Building 3 Brownlow Street Liverpool L69 3GL Tel: +44 (0) 151 794 8935 Fax: +44 (0) 151 794 8010 Email: louise.handley@liv.ac.uk	**Alexander Needham** Liverpool Clinical Trials Centre University of Liverpool 1st Floor, Block C Waterhouse Building 3 Brownlow Street Liverpool L69 3GL Tel: +44 (0)151 795 7505 Email: A.Needham2@liverpool.ac.uk	**Kayley Tyrell** Liverpool Clinical Trials Centre University of Liverpool 1st Floor, Block C Waterhouse Building 3 Brownlow Street Liverpool L69 3GL Tel: +44 (0) 151 795 5291 Fax: +44 (0) 151 794 8010 Email: Kayley.Tyrell@liverpool.ac.uk

Contact Details: Independent Oversight Committees

Independent Safety and Data Monitoring Committee (ISDMC)		
Independent Statistician **Dr Caroline Kelly** Cancer Research UK Clinical Trials Unit Glasgow The Beatson West of Scotland Cancer Centre Level 0, 1053 Gt. Western Road Glasgow G12 0YN Tel: +44 (0) 141 301 7188 Fax: +44 (0) 141 301 7189 Email: Caroline.Kelly@glasgow.ac.uk	**Independent Clinician (Chair)** **Dr Mark Middleton** Consultant Medical Oncologist University of Oxford Department of Medical Oncology Churchill Hospital Oxford OX3 7LJ Tel: +44 (0) 1865 235 313 Fax: +44 (0) 1865 235 982 Email: mark.middleton@oncology.ox.ac.uk	**Independent Clinician** **Dr Louise Medley** Consultant Medical Oncologist Torbay and South Devon NHS Foundation Trust Lawes Bridge Torquay TQ2 7AA Tel: +44 (0) 1803 655 643 Fax:+44 (0) 1803 655 386 Email: louise.medley@nhs.net

Independent Members of the Trial Steering Committee (TSC)		
Chairman **Dr Richard Carvajal** Columbia University Medical Center 177 Ft Washington Avenue New York NY 10032 Tel: 646-317-6354 Fax: 212-305-6891 Email: carvajalr@columbia.edu	**Independent Statistician** TBC	**Lay member** c/o Louise Handley

Table of Contents

Glossary

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CTU	Clinical Trials Unit
GP	General Practitioner
IB	Investigator's Brochure
ISDMC	Independent Safety and Data Monitoring Committee
IMP	Investigational Medicinal Product
MREC	Multi-centre Research Ethics Committee
PI	Principal Investigator
R&D	Research & Development
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
TC	Trial Co-ordinator
DM	Data Manager
PIS	Patient Information Sheet
ICF	Informed Consent Form
SOP	Standard Operating Procedure

1 PROTOCOL SUMMARY

Title: SelPac: A randomised, three arm, open label, phase II study comparing continuous single agent Selumetinib to combination paclitaxel and selumetinib in either a continuous or intermittent schedule.

Phase: II

Target Disease: Metastatic uveal melanoma

Sample Size: 72 evaluable patients are to be randomised

Number of Sites: 13 sites in the UK and 1 site in Germany

Study Duration: The planned treatment duration per patient will be until progression of disease, unacceptable toxicity or withdrawal of consent. For patients in arm B and C, paclitaxel treatment will be discontinued after a maximum of 6 cycles, with patients continuing on selumetinib alone. Participation in the study will be until withdrawal of consent or death.

Patients who stop treatment before having developed progressive disease (PD) will be assessed every 8 weeks for response until PD.

Overall study duration is approximately 42 months.

Study Arms: Arm A: Selumetinib orally at 75mg twice a day, continuously.

Arm B: Paclitaxel IV at 80mg/m^2, administered on day 1, 8 and 15 for a maximum of 6 cycles, with 75mg selumetinib orally twice a day, continuously during and after paclitaxel treatment.

Arm C: Paclitaxel IV at 80mg/m^2, administered on day 1, 8 and 15 for a maximum of 6 cycles, with 75mg selumetinib orally twice a day with 2 days off prior to (and the morning of) each paclitaxel infusion, and given continuously after completion of paclitaxel.

Endpoints:

Primary Endpoint

- Progression Free Survival time

Secondary Endpoint(s)

- Overall Survival time
- RECIST Response
- Safety and toxicity

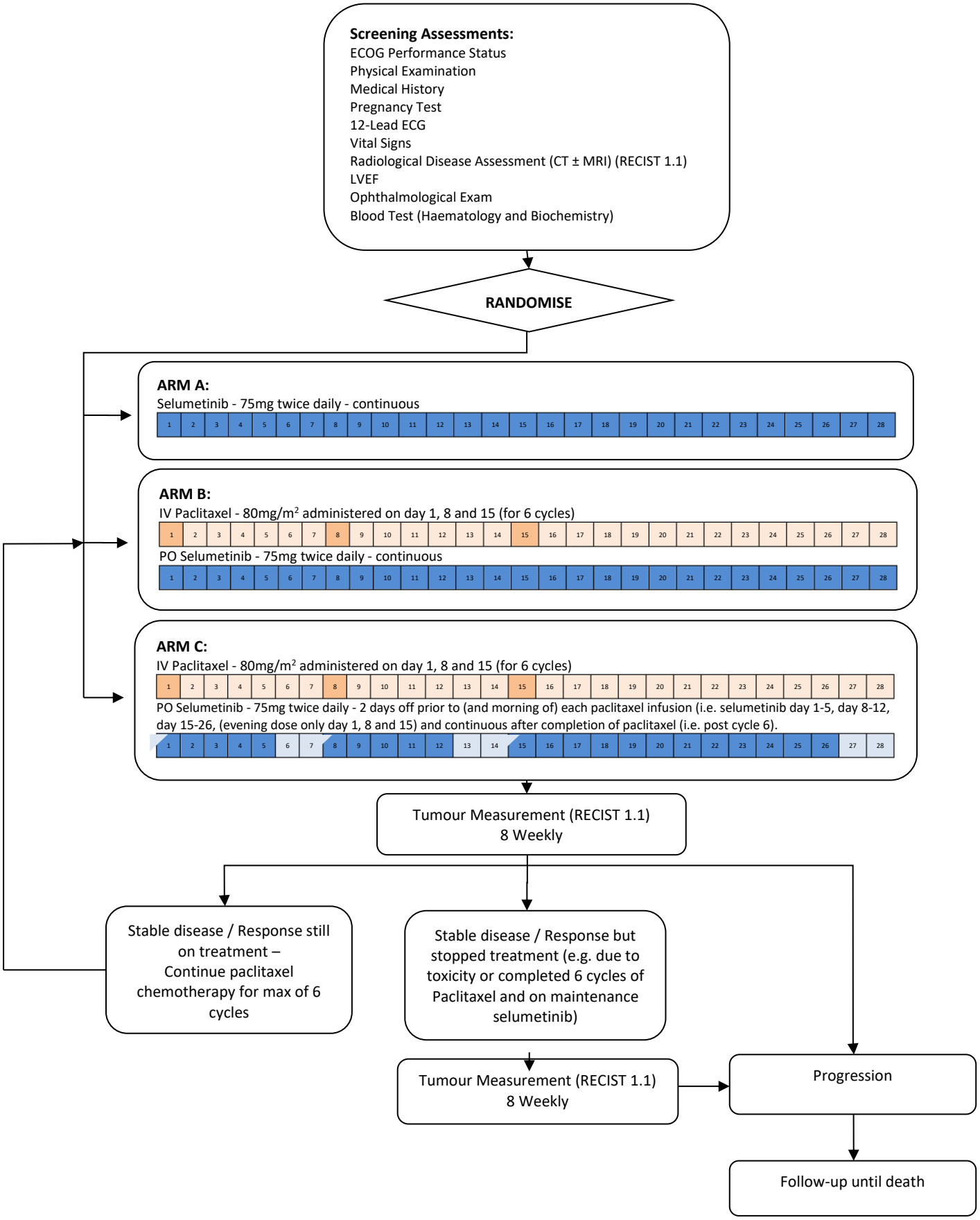
Exploratory Endpoints

Exploratory endpoints will include, but not be confined to:

- GNAQ/GNA11 mutation status
- MEK transcriptional signature

Protocol Summary - continued

Schematic of Study Design:



2 BACKGROUND INFORMATION

2.1 Introduction

Uveal melanoma (UM) is a rare disease with an incidence of about 1 per 100,000 (Keenan et al., 2012), affecting approximately 500 people per year in the UK. 50% of all patients will relapse with metastatic disease and unfortunately the prognosis for relapsed patients is poor with a median overall survival (OS) of around 6 months (Kujala et al., 2003). The disease has a distinct biology, clinical course and behaviour when compared to cutaneous melanoma(Luke et al., 2014). It is hepatotropic and resistant to conventional chemotherapy. In addition, due in the main to the rarity of uveal melanoma, the majority of clinical trials have been either phase I, or single arm phase II studies, and to date there is no proven standard of care.

Patients with metastatic UM are commonly treated with either the chemotherapy agent dacarbazine or the anti-CTLA4 antibody, ipilimumab. However, this is principally a reflection of practice in the management of cutaneous melanoma, and there is limited evidence to support use of either treatment in UM. In a recent, randomised, phase II clinical trial that compared sunitinib with dacarbazine, the response rate for dacarbazine was only 8% and median progression free survival (PFS) and overall survival (OS) were 2.8 and 7.4 months respectively (Sacco et al., 2013). No responses were seen in the sunitinib arm, and median PFS and OS were not statistically different (2.8 and 6.3 months respectively).

Ipilimumab is an immune checkpoint inhibitor that has shown significant activity in cutaneous melanoma (Hodi et al., 2010). While there have been no randomised studies in UM, retrospective analyses suggest that ipilimumab is less efficacious in UM. In one study, which reported clinical experience in 39 patients treated with ipilimumab, there was only one response, with a further delayed response to give an overall response rate of 5.1%. 46% of the patients had either a response or stable disease at 3 months, and overall survival was 9.6 months (Khan et al., 2012).

There is therefore a clear need for the assessment of novel therapies in metastatic UM, with a prime example being agents that target the MAPK signalling pathway. This is almost invariably activated in UM, although, unlike cutaneous melanoma, this is not through the oncogenes RAS or BRAF but rather through mutations in the heterotrimeric G-protein subunits GNAQ and GNA11. Mutations in these two genes are mutually exclusive and occur in around 90% of all cases (Onken et al., 2008, Van Raamsdonk et al., 2010). Preclinical work has shown that GNAQ or GNA11 mutant UM cell lines are sensitive to inhibition of the MAPK pathway using MEK inhibitors (Ambrosini et al., 2012). In addition, a recent phase II study has shown that inhibition of MEK is clinically active in UM (Carvajal et al., 2014).

MEK inhibition therefore holds significant promise in uveal melanoma, and it is quite possible that this will become a standard of care. A company sponsored registration study with selumetinib in combination with dacarbazine (SUMIT) and an International Rare Cancer Initiative (IRCI) study with trametinib both opened in 2014. The former will complete recruitment by the end of 2014, while the latter did not open in the UK. The current study, which will assess the relative merits of MEK inhibition alone or in combination with chemotherapy in one of two schedules, will follow on from the registration study and is planned to occupy the whole of the UK network for a further 2 years.

2.2 Rationale

Selumetinib (previously known as AZD6244 and ARRY-142886) is a potent inhibitor of mitogen activated protein kinases (MEK), that abrogates the ability of MEK to phosphorylate extracellular signal-regulated kinase (ERK) 2 with an IC50 of 10-14nM in in vitro enzyme assays (Wallace et al., 2004). Selumetinib is selective for MEK and is inactive or minimally active against a panel of other kinases (Wallace et al., 2004). Work in cell lines has shown selumetinib inhibits proliferation in cell lines which exhibit constitutively active MAPK signalling due to either mutations in RAS or BRAF (Davies et al., 2007).

As described in section 2.1 above, activation of the MAPK pathway is a common finding in uveal melanoma, where it is driven by mutations in either GNAQ or GNA11, and leads to increased sensitivity to MEK inhibitors (Ambrosini et al., 2012). This led to the instigation of a randomised phase II clinical trial comparing selumetinib with temozolomide or dacarbazine, which reported earlier this year (Carvajal et al., 2014). Half of the patients (50%) who received selumetinib experienced some reduction in metastatic disease burden in comparison to 11% of patients receiving chemotherapy. 15% of patients on the selumetinib arm had a partial response by RECIST criteria, compared with none in the chemotherapy, and the median PFS for selumetinib was 15.9 weeks in comparison with 7 weeks for chemotherapy (HR 0.46, p=0.0005) (Carvajal et al., 2014). Patients who were allowed to cross over to the selumetinib arm appeared to have less benefit than those who were treatment naïve. Notably, this was the first trial of a systemic therapy to demonstrate a significant improvement in PFS in uveal melanoma. The Phase III SUMIT study however randomising selumetinib + dacarbazine vs dacarbazine failed to show a statistically significant improvement in PFS.

In the current study we therefore intend to investigate whether the addition of the microtubule stabilising agent, paclitaxel will lead to increased and more durable responses to treatment. This is based on preclinical evidence that the combination of a MEK inhibitor and a taxane demonstrates significant induction of apoptosis (MacKeigan et al., 2000, McDaid et al., 2005, Xu et al., 2009). Taxane induced activation of the MEK/ERK pathway is associated with cell survival: activation of ERK1/2 results in degradation of the BH3-only protein Bim and phosphorylation of Bad, inhibiting apoptosis(Taxman et al., 2003).

This pre-clinical evidence demonstrating the potential advantage of combining a MEK inhibitor with a taxane has underpinned two industry/NCRI studies in advanced cutaneous melanoma (DOC-MEK and PACMEL), both of which were CTAAC approved. DOC-MEK has reported a non-significant trend in favour of selumetinib combined with docetaxel compared to docetaxel alone with improved response rate (31.7% vs 14.3% p=0.059) and PFS (4.23 months vs 3.93 months HR 0.753 p=0.13)(Gupta et al., 2014). PACMEL, which compares the MEK inhibitor trametinib in combination with weekly paclitaxel with weekly paclitaxel alone is ongoing.

Both of these studies examine the utility of combination treatment in BRAF wild-type melanoma in which it is known that the MAPK pathway is activated but in which, other than NRAS, driver mutations have not been identified. Because of the high incidence of GNAQ/GNA11 mutations in uveal melanoma, the MAPK pathway is constitutively active. The fact that single agent MEK inhibition with selumetinib appears more clinically active in uveal melanoma than within the BRAF wild-type cutaneous population may reflect this (Kirkwood et al., 2012, Carvajal et al., 2014) Because uveal melanoma appears more sensitive to single agent MEK inhibition than BRAF wild-type cutaneous melanoma, it is possible that the MEK / taxane combination is more active in uveal melanoma. Indeed, greater improvements in PFS were seen for MEK combinations over single agent chemotherapy in BRAF mutant melanoma (Robert et al., 2013) and RAS mutant non-small cell lung cancer (Janne et al., 2013).

While there is limited evidence of clinical activity for single agent paclitaxel in UM, it has been used relatively frequently in the treatment of metastatic uveal melanoma in clinical practice. There has in

addition has been a single arm phase II study which investigated a modified form of paclitaxel, docosahexaenoic acid-paclitaxel, in 22 patients, in which 1 patient had a partial response, 7 had stable disease at 3 months, and the overall survival was 9.8 months (Homsi et al., 2010).

Pre-clinical evidence suggests that scheduling of the MEK inhibitor / taxane combination may influence the potency of the combination. Withdrawal of MEK inhibition before exposure to the taxane significantly enhanced cell kill (Holt et al., 2012), presumably because of initiation of cellular proliferation. We have therefore designed this study with weekly paclitaxel (3 weeks out of 4) to best test the hypothesis that withdrawal of MEK inhibition prior to chemotherapy exposure increases cell kill.

Rationale for doses

For each arm the IMP dosing is as follows:

Arm A PO Selumetinib - 75mg twice daily - continuous

Arm B PO Selumetinib - 75mg twice daily - continuous
IV Paclitaxel - 80mg/m^2 administered on day 1, 8 and 15 (for 6 cycles)

Arm C PO Selumetinib - 75mg twice daily - 2 days off prior to (and morning of) each paclitaxel
IV Paclitaxel - 80mg/m^2 administered on day 1, 8 and 15 (for 6 cycles)

The rationale for the doses is to investigate whether the combination of selumetinib (arm B and C) with weekly paclitaxel has significant superior clinical activity to selumetinib alone (arm A).

The two combination arms of selumetinib in either a continuous (arm B) or intermittent schedule (arm C) with weekly paclitaxel will best test the hypothesis that withdrawal of MEK inhibition prior to chemotherapy exposure increases cell kill.

The three arm randomised phase II design has been selected as most appropriate to detect whether there is a strong enough clinical signal to warrant further investigation of combination selumetinib/chemotherapy in either continuous or intermittent schedules.

Selumetinib (used as single agent or in combination) will be given at the recommended dose for selumetinib studies of 75mg twice daily continuous dosing. A full description on the recommended dose for selumetinib studies is detailed in the selumetinib IB.

Selumetinib has not previously been combined with paclitaxel. However, full dose selumetinib has been combined successfully with docetaxel, a more toxic drug than paclitaxel, in the DOC-MEK study. In addition, trametinib (a MEK inhibitor with a longer half-life than selumetinib and therefore a likely greater potential for DLT in combination) has been successfully combined at full dose with weekly (3 out 4 weeks) paclitaxel at 80mg/m^2 in the PACMEL trial. We therefore believe it is highly likely that full dose selumetinib (75mg bd po) will be tolerable in combination with weekly paclitaxel. If dose reductions are required, the paclitaxel dose may be reduced to 60mg/m^2.

Rationale for exploratory endpoints and translational research

A key paradigm in the development of targeted therapies is the requirement for robust biomarkers that enable the selection of patients most likely to respond to treatment. In this study we aim to assess two potential biomarkers that may predict for response to MEK inhibitors; namely GNAQ/GNA11

mutations and a MEK sensitivity/resistance signature. As described above, mutations in GNAQ and GNA11 lead to activation of the MAPK pathway, and it may be hypothesised that these would predict for sensitivity to MEK inhibitors. In the study by Carvajal et al, patients with mutations in GNAQ or GNA11 exon 5 did not demonstrate improved clinical benefit compared to wild type patients (Carvajal et al., 2014). However, data that were published after study initiation suggest that mutations in exon 4 may also contribute to activation of the MAPK pathway (Van Raamsdonk et al., 2010), and of 5 patients who were wild type for exon 5 and for whom tissue was available for further analysis, exon 4 mutations were identified in 3 patients, one of whom had a major response to selumetinib (Carvajal et al., 2014). In the current study we will therefore assess for both exon 4 and exon 5 mutations in GNAQ and GNA11. However, over 90% of patients are likely to have mutations in GNAQ/GNA11 and even if these mutations predict for response there is a clear need to identify further biomarkers that will enable patient stratification.

In the second exploratory endpoint, we aim to use a transcriptional signature that was previously developed using an unbiased approach that assessed differential gene expression in selumetinib sensitive and insensitive cell lines from a panel of over 100 cell lines, with further extensive validation in an independent set of cell lines, xenografts and FFPE melanoma samples (Dry et al., 2010). This assay will be evaluated to determine if it could be used for stratification of patients by functional activation status of MEK in future studies. A similar assessment is being made as part of a study of cutaneous melanoma (PACMEL) and the data will be combined in the final evaluation. The assay utilises the nCounter analysis system from nanoString technologies and may be performed on paraffin embedded tissue. The assay has not previously been assessed in uveal melanoma. However, prior to use on SelPac samples, RNA extraction and the nanostring assay will be optimised using samples obtained from the SUMIT study.

The study will also enable the collection of samples that will allow for future sequencing analysis that would enable a broader assessment of genetic predicates for MEK sensitivity. Such samples may also be used for assessment of other predictive biomarkers that may be developed during the course of the trial. In addition, where available, we will request samples from biopsies and enucleations of primary malignancies to enable future work into paired primary and metastatic disease. Biopsies at progression may also be undertaken, following discussion between the investigator and patient and subject to separate consent. Serial blood samples that will enable the investigation into circulating tumour DNA and exosomes will also be collected. A separate protocol will describe the translational research in more detail.

2.3 Objectives

To determine:

a) Whether there is sufficient evidence that the combination of selumetinib weekly paclitaxel (in either a continuous or intermittent schedule) is superior to selumetinib alone, justifying a subsequent phase III trial.

b) The prognostic and predictive effects of tumour genotype (GNAQ/GNA11 mutation status) or MEK transcriptional signature (assayed using nCounter analysis system).

2.4 Identified Risks and Known Potential Benefits

2.4.1 Identified Risks

Identified risks relate to the treatment with selumetinib alone or in combination with paclitaxel. The most common adverse events with selumetinib monotherapy (75mg bd po) include acneiform rashes, diarrhoea, nausea, vomiting, peripheral oedema and fatigue. Stomatitis, dry skin and pyrexia have also been commonly reported in studies of selumetinib.
Central serous retinopathy/retinal pigment epithelial detachment (CSR/RPED) and retinal vein occlusion have been reported in a small proportion of patients, as a consequence of which patients will undergo ophthalmological review at outset or in the event of blurred vision or other ophthalmological symptoms (section 6.1). Similarly, reductions in left ventricular ejection fraction (LVEF) have been reported and patients will have regular assessment of LVEF during treatment (section 6.1). A full description of adverse events is detailed in the investigators brochure (IB) for selumetinib.

Weekly paclitaxel is generally well tolerated, with the main adverse events being haematological toxicities (neutropaenia, anaemia, thrombocytopaenia), fatigue, nausea or vomiting, arthralgia, neuropathy, allergic reactions and hair loss (see SmPC for details). As discussed in section 2.2, selumetinib has not previously been combined with paclitaxel, however full dose selumetinib has been combined successfully with a different taxane, docetaxel (DOC-MEK), a more toxic drug than paclitaxel. We anticipate that the side effects of paclitaxel in combination with selumetinib will be similar to those of selumetinib/docetaxel, which are detailed in the selumetinib IB.

2.4.2 Known Potential Benefits

There are currently no licenced, effective treatments available for metastatic uveal melanoma. The study by Carvajal et al (Carvajal et al., 2014) has shown that selumetinib may lead to an increase in PFS in this patient group. This finding, subject to confirmation in a further study, suggests that MEK inhibition may improve clinical outcome in this patient group for which there is an unmet clinical need. All patients in the current study will receive selumetinib, from which they may benefit. In addition, two thirds of patients will additionally receive paclitaxel. While the additional benefits of this are currently unknown, the hypothesis of the study is that the addition of paclitaxel may lead to increased response rates and/or duration of response.

3 STUDY POPULATION

3.1 Inclusion Criteria

1. Histologically or cytologically confirmed metastatic uveal melanoma from a metastatic site.
2. Patients must have measurable disease, defined by RECIST 1.1.
3. Age ≥18 years.
4. ECOG performance status 0-2.
5. Life expectancy of greater than 3 months.
6. Able to swallow and retain orally-administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels.
7. All prior treatment-related toxicities must be CTCAE v4 grade ≤1 (except alopecia and endocrinopathies treated with hormone replacement) at the time of randomisation.
8. Laboratory values as listed below (SI units):
    - Total bilirubin ≤1.5 x institutional upper limit of normal (ULN).
    - Aspartate aminotransferase or alanine aminotransferase <2.5 x ULN (or ≤5 x ULN in presence of liver metastases).
    - Haemoglobin ≥90 g/L.
    - Platelets >100 $x10^9$/L (100,000 per mm^3).
    - Absolute neutrophil count >1.5 $x10^9$/L (1500 per mm^3).
    - Creatinine ≤132.6 µmol/L OR calculated creatinine clearance (Cockroft-Gault formula) ≥50 mL/min OR 24-hour urine creatinine clearance ≥50 mL/min.
9. Female patients of child-bearing potential should have a negative pregnancy test.
10. Written (signed and dated) informed consent.

3.2 Exclusion Criteria

1. Patients may not have received prior chemotherapy for uveal melanoma. This includes patients who have received isolated hepatic perfusion of chemotherapy. Patients who have received prior immunotherapy or non-chemotherapy locoregional therapy for liver metastases, but who have documented evidence of progression of metastatic disease would however be eligible.
2. Patients who have a known or suspected brain or leptomeningeal metastases, or spinal cord compression, unless asymptomatic, has been treated with surgery and / or radiation, and has been stable without requiring corticosteroids or anti-convulsant medications for at least 4 weeks prior to the first dose of study medication.
3. Prior exposure to MEK, Ras, or Raf inhibitors or history of hypersensitivity to any excipient agents.
4. History of another malignancy unless disease-free for 3 years. Patients, who have had a completely resected non-melanoma skin cancer, are eligible.
5. Any permitted previous treatment must have been greater than 21 days prior to study treatment starting.
6. Current use of a prohibited medication (refer to **Appendix 9**).
7. Cardiac conditions as follows:
    - Uncontrolled hypertension (BP ≥150/95 mmHg* despite medical therapy)

    *For German-patients please refer to the international research site group-specific appendix to the protocol regarding uncontrolled hypertension criteria.
    - Acute coronary syndrome within 6 months prior to starting treatment.

- Baseline left ventricular ejection fraction (LVEF) below the LLN or <55% measured by echocardiography or institution's LLN for MUGA.
- Atrial fibrillation with a ventricular rate >100 bpm on ECG at rest.
- Symptomatic heart failure NYHA Class II-IV, prior or current cardiomyopathy, or severe valvular heart disease (refer to **Appendix 1**).
- Prior or current cardiomyopathy including but not limited to the following:
  - Known hypertrophic cardiomyopathy.
  - Known arrhythmogenic right ventricular cardiomyopathy.
  - Previous moderate or severe impairment of left ventricular systolic function (LVEF <45% on echocardiography or equivalent on MUGA) even if full recovery has occurred.
- Uncontrolled angina (Canadian Cardiovascular Society grade II-IV despite medical therapy, refer to **Appendix 2**).
- Acute coronary syndrome within 6 months prior to starting treatment.
- QTcF >450ms or other factors that increase the risk of QT prolongation.

8. Ophthalmological conditions as follows (unless in the eye involved by uveal melanoma):
   - Intra-ocular pressure >21 mmHg, or uncontrolled glaucoma (irrespective of intra-ocular pressure).
   - Current or past history of retinal pigment epithelial detachment (RPED)/central serous retinopathy (CSR) or retinal vein occlusion.
9. Uncontrolled intercurrent illness or uncontrolled systemic disease including, but not limited to, ongoing or active infection – including any patient known to have hepatitis B, hepatitis C or human immunodeficiency virus (HIV), symptomatic congestive heart failure, unstable/uncontrolled angina pectoris, uncontrolled cardiac arrhythmia, QTc prolongation, active bleeding diatheses, renal transplant or psychiatric illness/social situations that would limit compliance with study requirements.
10. Female patients who are breast-feeding.
11. Male or female patients of reproductive potential who are not employing effective methods of contraception*
    *For German-patients please refer to the international research site group-specific appendix to the protocol for further instruction.
12. German-patients who are placed on administrative order in an institution or are dependant from the sponsor or study doctor are excluded from the study (applicable to the German site only).

3.3 Patient Transfer and Withdrawal

In consenting to the trial, patients are consented to trial treatment, follow-up and data collection. If voluntary withdrawal occurs, the patient should be asked to allow continuation of scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the subject's condition becomes stable.

It may also be necessary to transfer patients to another participating centre to continue their involvement in the trial.

Patients should be asked to allow continuation of scheduled evaluations (follow up) and be given appropriate care under medical supervision. Follow-up of these patients will be continued by the trial centre team, the Principal Investigator at the trial centre, and where these are unsuccessful, through the patient's GP if appropriate.

3.3.1 Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient or for follow-up via GP.

A copy of the patient CRFs should be provided to the new site. The patient will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre. The LCTC should be notified in writing of patient transfers.

3.3.2 Withdrawal from Trial Intervention

Patients **must** withdraw from treatment for any of the following reasons:

- Patient withdraws consent
- Disease progression
- Unacceptable toxicity
- Pregnancy

Patients **may** be withdrawn from treatment for any of the following reasons:

- Physician choice – e.g. intercurrent illnesses preventing further treatment, poor compliance to the study protocol.

If a patient is withdrawn from study treatment, they will be treated according to usual local clinical practice. The reason(s) for withdrawal from study treatment will be captured on the end of treatment form and sent to the LCTC.

3.3.3 Follow-up

Patients who have discontinued study treatment will be followed up on an 8-weekly basis until death.

Follow-up visits should be scheduled alongside the planned CT (± MRI) scan schedule which follows the same 8-weekly schedule. This scheduling is also applicable for patients who have progressed and do not need any further scans but remain on follow-up for survival.

Centres should explain the importance of remaining on the trial for follow-up visits, or alternatively allow routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the patient explicitly withdraws from the trial completely (see section 3.3.4).

3.3.4 Withdrawal from Trial Completely

For patients who are withdrawn from study treatment, and who wish to withdraw from the trial completely, the end of study form must be completed indicating that they choose to withdraw from the trial completely. Any anonymised data collected up to the point of the withdrawal from the trial will be included in the data analysis for the trial. The LCTC must be informed of any patient who withdraws from the trial completely by receiving a copy of the end of study form.

4 ENROLMENT AND RANDOMISATION

4.1 Screening

Screening will be performed upon a patient's possible eligibility for the study and must be documented on the LCTC web portal "Screening and Enrolment log". Screening details should be entered into the portal and this will automatically generate a screening number and a confirmation email with these details will be sent to site staff. The screening log can be printed at any time off the Portal to allow for storage in the Investigator Site File. Step-by-step guides will be issued to research site staff and the process will also be demonstrated during site initiations.

The following screening assessments must be performed within 28 days prior to randomisation:

- **Written Informed Consent**
- **Radiological Disease Assessment** (RECIST version 1.1)
  - All patients will undergo a CT scan of the chest and abdomen. The liver and adrenal glands should be included in the field of view. Any other anatomical sites where disease is suspected or known should also be imaged at baseline.
  - Radiological assessments should be performed using computerised tomography (CT) scanning; however additional liver magnetic resonance imaging (MRI) may be carried out for assessment of liver metastases if measurable disease is not clearly defined on screening CT.
  - If a patient has undergone MRI scan to determine measurable lesions at baseline assessment, they should continue to receive MRI scanning to measure the target lesions.
  - Medical imaging may also be required if a patient deteriorates in-between the tumour assessment (8-weekly) visits. Medical imaging must always be 8-weekly irrespective of clinic assessment and treatment schedules and should be taken from treatment start date.
- **Ophthalmological Exam**
- **Left Ventricular Ejection Fraction (LVEF)** - either ECHO or MUGA can be used to measure LVEF, but the same technique should be used for all patients at site throughout study.
- **Collection of one blood sample** (approx. 20ml) for translational research[1]

[1] If the translational blood sample is omitted in error at the screening visit, the baseline sample may be taken pre-treatment on day 1 instead. Translational blood samples taken from screen fail patients will still be collected. Translational research samples are to be collected only if the patient consents (patients who decline translational research are still eligible for protocol treatment).

The following screening assessments must be performed within 7 days prior to randomisation:

- **ECOG Performance Status** must be assessed and must be 0-2.
- **Physical Examination** including vital signs
  - Physical examination includes an assessment of the following: general appearance, respiratory, cardiovascular, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, abdomen, musculo-skeletal (including and extremities) and neurological systems.
  - Measurement of weight and height.
  - Temperature.
  - Blood pressure.
- **Urine or Serum Pregnancy Test** (women of child-bearing potential only).
- **Electrocardiogram**
  - A single 12-lead ECG should be performed and will be analysed locally.

- Patients should be supine and at rest 10 minutes prior to recording the ECG.
- The PI or designated physician will review each of the ECG(s) and may refer to a local cardiologist if appropriate.
- Parameters including heart rate, duration of QRS complex, RR, PR and QT intervals will be collected. QT interval correcting using Friderica's formula (QTcF) should be calculated.
- If an abnormal ECG finding at the screening assessment is considered to be clinically significant by the Investigator, it should be reported as a concurrent condition.

- **Haematology**
- **Biochemistry** (to include urea, Cr, Na, K, Ca, Alb, Bili, ALP, ALT (or AST), Phosphate, GGT and LDH, troponin (at baseline)).

  - Creatinine or Creatinine Clearance: only one test needs to be reported, the same test must however be consistently reported throughout the study.
  - ALT or AST: only one test needs to be reported, the same test must however be consistently reported throughout the study.
  - GGT is required at screening and day 1 of each cycle and does not need to be collected on day 8 or day 15.

Patients who meet the inclusion criteria (see section 3.1) following completion of screening assessments will then be eligible for randomisation.

4.2 Enrolment / Baseline

Patients who have given informed consent and have been found to comply with all inclusion and exclusion criteria will be randomised by trained staff at the LCTC.

For randomisation to study treatment, the following documents must be submitted by fax to the LCTC (for the anonymised reports add screening number and initials as identifiers):

- Randomisation form
- Signed informed consent form
- Anonymised screening blood test results
- Anonymised ECHO or MUGA report
- Anonymised pathology report (metastatic diagnosis)
- Anonymised radiological disease assessment scan report (RECIST 1.1) (CT ± MRI)

Randomisation – Tel: 0151 794 8935/795 5291 Fax: 0151 794 8010

(Between 08:00 – 16:00, Monday - Friday, excluding public and university holidays)

The LCTC operates an electronic system (DatAnywhere) for secure transfer of documentation, this can be used as an alternative to fax based submission. If this system is required, sites will be provided with the appropriate work instruction.

Personnel from the LCTC will review the documents; confirm eligibility and record essential demographic data. The patient will then be randomly allocated a trial treatment and given a unique trial number through an IWRS (interactive web response system). The randomisation form will be annotated with details of the kit number(s) and the patient trial number and returned by fax/email to

the investigator at site. The IWRS system will also send confirmation of randomisation and kit numbers to all site staff.

The trial number should be filled in on each subsequent page of the patients CRF.

Each centre will be provided with kits of packaged drugs, the kit number allocated to the patient will only be available at that centre.

Trial treatment should start within 7 days of randomisation.

5 TRIAL TREATMENTS

5.1 Introduction

Baseline radiographic assessment of disease will be performed within 28 days prior to randomisation. Once a patient has been randomised, a date for their first treatment (day 1) visit must be arranged. Day 1 must take place within 7 days of randomisation (≤ 7 days).

Paclitaxel: Patients randomised to Arm B and C will be administered 80mg/m^2 of paclitaxel days 1, 8, 15 of a 4 week cycle, for a maximum of 6 cycles.

Selumetinib: Patients will receive orally at 75mg twice a day continuously on both Arm A and B.

Patients on Arm C will have two days off selumetinib prior to (and the morning of) receiving each administration of paclitaxel chemotherapy (i.e. selumetinib will be taken on day 1 - 5, day 8 - 12, day 15 - 26 of each cycle, with the morning dose omitted on days 1, 8 and 15). And given continuously after completion of paclitaxel.

Patients allocated to Arm A will be given selumetinib to take continuously and will only be required to visit hospital once each cycle (one cycle is 4 weeks).

Patients allocated to Arm B and Arm C will attend clinic once weekly, for 3 weeks each cycle for a paclitaxel infusion, the fourth week will be a rest week. If patients are still on treatment after completing 6 cycles, the paclitaxel will be stopped and patients will continue on selumetinib alone, and will then only be required to visit hospital once each cycle (one cycle is 4 weeks).

5.2 Paclitaxel

5.2.1 Formulation, Packaging, Labelling, Storage and Stability

Commercially available paclitaxel will be used in this study and will be supplied from existing hospital stocks and will not be supplied as part of this study. Participating sites must state which brand of paclitaxel they will use before their site is initiated.

Manufacturer:	Generic paclitaxel will be sourced by local pharmacies following their usual local practice. The manufacturers should have an appropriate marketing authorisation in place, the details of which may be found on the following websites: emc.medicines.org.uk www.mhra.gov.uk
Formulation:	Concentrate for solution for infusion.
Packaging, storage and stability:	Please refer to the specific SmPC for individual product.
Supplier's name:	The local hospital pharmacy.
Active Ingredient name/dose:	Paclitaxel 80mg/m^2 days 1, 8, 15.

5.2.2 Preparation, Dosage and Administration of Study Treatments

Paclitaxel will be supplied and prepared according to local policy. Paclitaxel must be handled and stored according to the instructions within the corresponding Summary of Products Characteristics (Please refer to current paclitaxel SmPCs supplied by the appropriate manufacturer).

Dose banding may be performed as per local practice.

Paclitaxel should be labelled as per standard hospital labelling procedures. For the purposes of this study an Annex 13 compliant label is required.

80mg/m^2 paclitaxel should be administered through an in-line filter with a microporous membrane ≤0.22µm.

All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to paclitaxel therapy.

Paclitaxel should be given under the supervision of a physician with experience in using cancer chemotherapeutic agents. Appropriate equipment for emergency treatment should be available.

5.2.3 Management of Hypersensitivity Reactions

Hypersensitivity to paclitaxel is a recognised complication, and may present with hypotension, facial flushing, back pain, dyspnoea, laryngeal and facial oedema and urticaria. If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require interruption of therapy. Hypersensitivity reactions should be managed according to local protocols, and paclitaxel may be re-introduced according to those protocols. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of paclitaxel and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with paclitaxel, but may continue with selumetinib within the study. Emergency management should be in line with local policy. The paclitaxel should be stopped, and oxygen, adrenaline, hydrocortisone, antihistamines and appropriate ventilatory and circulatory support administered if necessary.

Depending on the severity of the reaction, at the Investigator's discretion and with appropriate monitoring and availability of resuscitation equipment, the patient may be rechallenged with paclitaxel following a hypersensitivity reaction. The following rechallenge schedule may be adopted:

- Dexamethasone 20mg iv 3 hours before administration on the day of treatment and 20mg iv 30 minutes prior to paclitaxel administration
- Ranitidine 50 mg iv 30 minutes prior to paclitaxel
- Chlorphenamine 10mg iv stat 30 minutes prior to paclitaxel.
- Paclitaxel given at 10% of the rate i.e. 25 ml per hour for 2 hours. If no further reaction is seen, then the rate may be increased to 50 ml per hour for 1 hour, then 75 ml per hour, then 100 ml per hour to complete the infusion. If less than 10% of the dose was administered initially, then rechallenge may take place with the full dose of paclitaxel. If more than 10% was administered then the chemotherapy should be represcribed with an appropriate dose reduction. If the rechallenge is more than 72 hours after the initial dose, then haematology and biochemistry needs to be reassessed to determine suitability.

On subsequent cycles following a rechallenge the same schedule should be followed in line with local policy. If hypersensitivity to paclitaxel recurs despite full premedication then the paclitaxel should be stopped.

5.2.4 Dose Modification and Management of Paclitaxel Toxicity

Patients may receive second and subsequent doses of paclitaxel on the scheduled day of treatment provided that they have an absolute neutrophil count >1.5x10^9/L and a platelet count >100x10^9/L, and no drug-related non-haematological toxicity of grade 3 or above.
Adverse events considered related to the administration of paclitaxel are listed in the Summary of Product Characteristics.

One reduction in the dose of paclitaxel, to 60mg/m^2/week, should be undertaken if any of the following apply in the preceding cycle and are considered related to paclitaxel:

- Grade 3 or 4 neutropenia complicated by sepsis (temperature >38.5°C or documented infection),
- Grade 4 neutropenia > 7 days duration,
- Grade 4 thrombocytopenia, or grade 3 thrombocytopenia complicated by haemorrhage,
- Grade 3 or 4 non-haematological toxicities that cannot be adequately controlled by optimization of supportive therapy (except fatigue of less than 2 weeks duration, changes in alkaline phosphatase and LDH, hyperglycaemia related to temporary steroid use and alopecia),
- Grade 3 or 4 peripheral sensory neuropathy of greater than 2 weeks duration.
- >2 week delay in re-treating with paclitaxel.

Treatment should not be reintroduced until the toxicity has resolved to grade 1 or less. If a dose reduction in paclitaxel has occurred, the dose should not be re-escalated at subsequent cycles.

Where there is a delay in re-treating with paclitaxel within a cycle this will be classed as a missed visit (e.g. one week delay at cycle 2 week 2, patient would re-start at cycle 2 week 3). If there is a delay in re-treating with paclitaxel between cycles, the patient should be started at the start of the subsequent cycle (e.g. one week delay at the start of cycle 3 week 1, patient should still re-start at cycle 3 week 1).

For Arm C priority should be given to interrupt selumetinib treatment prior to paclitaxel including if the paclitaxel dose is delayed/deferred. Selumetinib dosing should be interrupted 2/7 before each dose of paclitaxel.

For arm B and arm C If paclitaxel is permanently discontinued, patients should continue with single agent selumetinib, for both arms selumetinib should then be taken in a continuous schedule.

Scan times do not shift and continue in accordance with the treatment start date (cycle 1 day 1) rather than cycles of treatment received.

In the case of neutropenic sepsis or grade 4 neutropenia greater than 7 days, paclitaxel can be restarted at the full dose, when appropriate but with G-CSF support (centres should follow local guidelines). If neutropenia recurs despite G-CSF, then the paclitaxel should be reduced to 60 mg/m^2. If G-CSF support cannot be offered a dose reduction in paclitaxel to 60 mg/m^2 should be applied. If the neutropenia then recurs then the paclitaxel should be stopped.

5.2.5 Paclitaxel – Specific Restrictions

There is no information on the use of paclitaxel in pregnant women. As with other cytotoxic drugs, paclitaxel may cause foetal harm in treatment of pregnant women. Therefore, paclitaxel must not be used during pregnancy unless clearly necessary. Women of childbearing potential should be advised to avoid becoming pregnant during treatment with paclitaxel, and to inform the treating physician immediately if pregnancy occurs.

Sexually active female and male patients of fertile age, and/or their partners, should use two reliable methods of contraceptive for at least 6 months after treatment with paclitaxel.

It is not known whether paclitaxel is excreted into human breast milk. Paclitaxel is contraindicated in lactating women. Breast-feeding should be interrupted during paclitaxel treatment.

5.3 Selumetinib

5.3.1 Formulation, Packaging, Labelling, Storage and Stability

Selumetinib is a potent, selective, allosteric inhibitor of MEK that is non-competitive with respect to ATP, licensed for development by AZ Pharmaceuticals from Array BioPharma, and currently in Phase III development for oncology indications.

Laboratory Name:	AZD6244
Formulation:	Blue hydroxylpropylmethylcellulose (HPMC) capsules.
Active Ingredient Name/Dose:	Selumetinib/25mg
Excipients:	Selumetinib Hyd-Sulfate and D-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS; a water-soluble form of Vitamin E).
Pack Size(s):	Capsules are supplied in white high density polyethylene (HDPE) bottles with foil-lined, induction sealed, child resistant closures. The container includes a desiccant canister.
Supplier's name:	Fisher Clinical Services.
Storage:	The capsules should be stored in their original packaging until use. For further information investigators should refer to the investigational product label.

Selumetinib will be provided to sites in labelled bottles, once the site has been activated by the Liverpool Cancer Trials Unit. The material will arrive at site ready to be dispensed to patients, local Pharmacy will need to confirm shipment of the drug to the site through the IWRS.

All investigator products must be kept in appropriate and secure storage conditions. A description of the appropriate storage and shipment conditions is specified on the investigational product label and investigator brochure. The stored study drug supplies must be accessible to authorized staff only. The storage area must also have adequate control of temperature in order to maintain stability and potency of study drug supplies.

5.3.2 Selumetinib – Specific Restrictions

The following restrictions should be included in studies of selumetinib:

- Patients should avoid excessive sun exposure and use adequate sunscreen protection if sun exposure is anticipated.
- Patients should not donate blood during the study and for at least 12 weeks after the last dose of selumetinib.
- During the studies, patients should avoid consuming grapefruits, Seville oranges, or any other products that may contain these fruits, e.g., grapefruit juice, **as these may effect selumetinib metabolism.**
- Unless considered clinically indicated, patients should avoid changes to, or the addition of, concomitant medications, in particular any that may affect the metabolism of selumetinib (e.g. CYP1A2, CYP2C19 or 3A4 inhibitors/inducers).

As reproductive toxicology data indicate that selumetinib has adverse effects on embryofoetal development and survival at dose levels that do not induce maternal toxicity in mice, the following restrictions apply:

- Selumetinib should not be administered to pregnant or breast-feeding women and conception while on treatment must be avoided. Female patients of child-bearing potential will be required to use two reliable methods of contraception for the duration of the study and until 4 weeks after the last dose of selumetinib.
- Male patients with sexual partners who are pregnant or who could become pregnant (i.e. women child bearing potential) should use two reliable methods of contraception for 3 months after the last dose of selumetinib to avoid pregnancy and/or potential adverse effects on the developing embryo.

Preliminary data (study D1532C00086) suggests that subjects of Asian descent may experience a higher exposure of selumetinib than the majority of subjects of non-Asian descent receiving an equivalent dose of selumetinib.

It is recommended that investigators take this information into consideration when dosing patients of Asian descent. If, during the course of the selumetinib development programme the dosing regimen being evaluated in this study is found not to be tolerated in a specific ethnic group, this ethnic group may later be excluded from this study. Investigators will be notified, and the protocol will be amended to reflect such findings. The data so far do not suggest a safety concern in any specific population.

5.3.3 Preparation, Dosage and Administration of Study Treatments

Selumetinib capsules will be taken orally, twice daily. It is recommended that selumetinib should be taken on an empty stomach - no food or drink other than water for 2 hours prior to dosing and 1 hour after dosing.

For Arm C selumetinib capsules will be taken orally twice a day with 2 days off prior to (and the morning of) each paclitaxel infusion i.e. on the days of paclitaxel administration (day 1, 8 and 15) the patient will receive the evening dose of selumetinib only. Selumetinib will be given continuously after completion of paclitaxel.

If a patient misses one or more doses of selumetinib, the patient should continue to take the treatment as per schedule, twice a day, and notify the study team looking after them that they have missed doses. If a patient misses one or more doses, an additional dose, or doses, should not be administered to account for the missed dose(s). Compliance with study treatment will be recorded in the CRF. If vomiting occurs the patient should not take another dose of selumetinib until the next scheduled dose (approximately 12 hours between doses).

5.3.4 Dose Modifications

The immediate management of any AE should be according to standard clinical practice for that event; for example anaemia should be managed by blood transfusion, and hypertension should be treated with appropriate anti-hypertensive medication. Subsequent management of treatment related AEs should be guided by the Investigators' assessment of causality.

Specific guidance for the management of AEs, interruption or reduction of treatment with selumetinib may be considered for particular events of special interest (i.e., diarrhoea, dyspnoea, rash, reduction in LVEF and visual disturbance), as indicated in the algorithms provided in Appendices. Some AEs (hyperphosphatemia and increase in calcium phosphate) should be managed according to local practice.

For all AEs reported in this study that are considered at least partly due to administration of selumetinib, the following dose reduction/adjustment guidance should be applied:

Treatment with selumetinib should be temporarily interrupted if one of the following AEs occurs despite optimal supportive care and is considered related to treatment with selumetinib:

- Any intolerable AE regardless of grade
- Any AE ≥CTCAE grade 3 (despite optimal supportive care)

On improvement of the AE to CTCAE grade 1 (or to CTCAE grade 2 for rash or to >LLN and within 10% of baseline for LVEF decreases) or baseline or within 4 weeks of onset (or within 6 weeks of onset for asymptomatic reductions in LVEF and for RPED/central serous retinopathy), selumetinib may be restarted at the same dose or may be reduced at the discretion of the Investigator. Step-wise dose reductions of selumetinib to **75 mg once daily, 50 mg twice daily, 50 mg once daily**, then permanent discontinuation, are allowed:

- If a <u>further episode of the same AE</u> subsequently requires dose interruption, selumetinib may be restarted at the next dose level down on improvement of the AE.

- If a <u>different AE</u> subsequently requires dose interruption, selumetinib may be restarted at the same dose or at the next dose level down on improvement of the AE.

If a patient discontinues selumetinib for more than 4 weeks (or more than 6 weeks for asymptomatic reductions in LVEF and RPED/central serous retinopathy), they are no longer eligible to re-start treatment.

Selumetinib should not be re-escalated to an earlier dose level on improvement of an AE. In the event of selumetinib dose interruption or reduction, the schedule of assessments described in the study plan should continue relative to the baseline visit.

All dose delays, reductions and adjustments will be recorded in the CRF.

Specific guidance for interruption or reduction of treatment with selumetinib may be considered for particular events, as indicated below.

For further information on the safety and tolerability profile of selumetinib, please refer to the latest version of the Investigator's Brochure.

5.3.5 Management of Specific Adverse Events Occurring During Treatment With Selumetinib

- Rashes: early initiation of treatment for rashes is strongly recommended to minimise the duration and severity of the adverse event (**Appendix 3**).
- Diarrhoea: early initiation of treatment for diarrhoea is strongly recommended to minimise the duration and severity of the adverse event (**Appendix 4**)**.**
- Reduction in LVEF: asymptomatic reductions in LVEF have been reported in some patients receiving selumetinib; treatment may be recommended depending on the magnitude of the LVEF reduction (**Appendix 5**).
- Dyspnoea (**Appendix 6**): new or worsening dyspnoea has been reported commonly during treatment with selumetinib; investigation to determine the underlying cause is recommended.
- Visual disturbances: symptoms, including blurred vision, occur commonly during treatment with selumetinib, and AEs of central serous retinopathy, retinal pigment epithelium detachment and retinal vein occlusion have been reported. Investigation to determine the underlying cause of visual disturbance is recommended (**Appendix 7**).
- Oral care: Patients should be made aware of the need for good oral care during studies with selumetinib (**Appendix 8**).

Table 1: Extra assessments are recommended for investigation of specific adverse events occurring during treatment with selumetinib:

Adverse event	**Assessment**
Clinically significant LVEF reduction (by ≥10% relative to baseline and to an absolute value below the institutions LLN)	**Single ECG and Troponin levels (isoform according to institutional norm). If Troponin assessments are not available, as per local practice, CK-MB should be assessed.**
Cardio-respiratory AEs of non-obvious cause	**Single ECG and Troponin levels (isoform according to institutional norm). If Troponin assessments are not available, as per local practice, CK-MB should be assessed.**
New or worsening respiratory symptoms (such as dyspnoea, cough)	**Single ECG**
Unexplained muscle weakness	**Neuromuscular examination, urine analysis and CPK measurement performed (with where possible an additional CPK-MM) and be managed according to local practice.**

5.4 Accountability Procedures for Study Treatments

The PI is fully responsible for the Investigational Medicinal Products (IMPs) at the trial centre. Both paclitaxel and selumetinib are classed as IMPs for the purposes of this clinical trial. Dispensing of study treatment may be delegated to the hospital pharmacy as locally applicable.

The person responsible for dispensing the study treatment will be responsible for maintaining adequate control of the IMPs and for documenting all transactions relating to them (as a minimum batch number, expiry date and dispensing date must be documented on the Drug Accountability Log). IMPs must be stored in a safe and secure place (only accessible to authorized personnel), and applicable Standard Operating Procedures (SOPs) must be followed.

5.5 Assessment of Compliance with Study Treatments

Administration of paclitaxel will be completed at the clinic visit and the dosing information will be written in the CRF.

To assess the compliance with selumetinib treatment, patients will be asked to return any unused capsules to their clinic visits. The quantity will be noted in the CRF and the excess study treatment returned to the pharmacy for destruction in line with local procedures. Patients will only be provided with selumetinib for one cycle at a time.

5.6 Concomitant Medications/Treatments

Selumetinib capsules contain D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS, a water-soluble form of vitamin E) as an excipient. The maximum dose of vitamin E patients may receive from selumetinib is approximately 215.4mg/day. Therefore:

- Patients should not take any supplemental vitamin E. High doses of vitamin E have been reported to cause bleeding and interrupt blood coagulation processes.
- Selumetinib should be administered with caution in patients who are also receiving concomitant coumarin anticoagulant medications, e.g. warfarin. These patients should have their INR monitored / anticoagulant assessments conducted more frequently and the dose of the anticoagulant assessments conducted more frequently and the dose of the anticoagulant should be adjusted accordingly.

5.6.1 Medications to Avoid With Trial Treatments

Paclitaxel

Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit (e.g. erythromycin, fluoxetine, gemfibrozil) or induce (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, efavirenz, nevirapine) either CYP2C8 or CYP3A4.

Selumetinib

Unless considered clinically essential, patients should avoid taking other additional non-study medications that may interfere with the study medications. In particular, patients should avoid medications that are known to either induce or inhibit the activity of hepatic microsomal isoenzymes

CYP1A2, CYP2C19 and CYP3A4, as this may interfere with the metabolism of selumetinib. See **Appendix 9** for a list of medications that should be avoided when taking selumetinib.

5.6.2 Data on Concomitant Medication

Data on concomitant medication will be collected at baseline, day 1 of each cycle, end of study treatment and at the time of SAE reporting.

5.7 Overdoses

Paclitaxel

There is no known antidote for paclitaxel overdose. In case of overdose, the patient should be closely monitored. Treatment should be directed at the primary anticipated toxicities, which consist of bone marrow suppression, peripheral neurotoxicity and mucositis.

Selumetinib

Inadvertent misdosing of selumetinib, such as administration of a higher dose than stated in the protocol, should be followed up and treated with appropriate supportive care until recovery.

5.8 Co-enrolment Guidelines

During participation in this trial, participants will not be allowed to take part in studies with investigational agents. Participation in non-interventional studies, which will not materially affect the use of study medication or confound any primary or secondary outcome measures, is allowed.

5.9 Supply of Selumetinib

Patients will continue to receive selumetinib for as long as they are registered on study, and that this date can be significantly after the primary data analysis.

6 ASSESSMENTS AND PROCEDURES

6.1 Selumetinib – Specific Assessments

The following laboratory sampling and safety monitoring procedures are recommended for inclusion in clinical study protocols for selumetinib:

- **Ophthalmological examination** at baseline and if an AE of visual disturbance (including blurring of vision) occurs during treatment with selumetinib.

  Examination should include best corrected visual acuity, intraocular pressure measurement, and slit-lamp fundoscopy. If these examinations indicate retinal abnormality, OCT scan should be considered if clinically appropriate.

  Patients with an ongoing retinal abnormality at the time of discontinuation of selumetinib should have a follow-up ophthalmological assessment approximately 28 days after discontinuation. This assessment is recommended to document reversibility, but should be performed only if the patient is fit enough to have an assessment.

- **Left ventricular ejection fraction (LVEF)** at baseline, at 12-weekly intervals and if signs or symptoms of deterioration in LVEF occur during treatment with selumetinib.

  LVEF assessments are to be performed every 12 weeks (±14 days) calculated from the treatment start date (cycle 1 day 1). Assessment times do not shift and continue in accordance with the treatment start date.

  Patients with an ongoing reduction in LVEF of ≥10% and to <55% at discontinuation of selumetinib should have follow-up LVEF, single ECG and vital sign assessments approximately 28 days after discontinuation. These assessments are recommended to document reversibility, but should be performed only if the patient is fit enough to have the assessment.

- **Troponin levels** (isoform according to institutional norm) at baseline and if clinically significant LVEF reduction (by ≥10% and below the institution's LLN) or a cardio-respiratory AE of non-obvious cause occurs during treatment with selumetinib.

6.2 Schedule of Trial Procedures

Study Procedure	Screening & Baseline		Rand	Randomised treatment (Repeat each 28 day cycle) Cycle 1 to Cycle 6			Continuous selumetinib Cycle 7 onwards	End of treatment	Follow up	End of study
Day	≤28 days	≤7 days	Day 0	Day 1	Day 8	Day 15	Day 1			
Visit Windows (days)				+/- 1 day	+/- 1 day	+/- 1 day	+/- 1 day	+/- 7 days	+/- 7 days	+/- 7 days
Informed Consent	X									
Inclusion/Exclusion Criteria		X								
Randomisation			X							
ECOG Performance Status		X[h]		X			X	X		
Medical History Review	X									
Physical Examination		X[h]		X			X	X		
Pregnancy Test[o]		X								
Radiological Assessment[a]	X			Every 8 weeks (±3 days from treatment start date)						
12-Lead ECG[b]		X								
Vital Signs		X[h]		X			X	X		
Haematology[c]		X[h]		X	X[j]	X[j]	X			
Biochemistry[c]		X[h]		X	X[j]	X[j]	X			
LDH Test		X								
Ophthalmological Exam[d]	X									
LVEF[e]	X			Every 12 weeks (±14 days from treatment start date)						
Troponin[f]		X								
Selumetinib Dispensing				X	Dispensed at the start of each 28 day cycle.		X			
Selumetinib Arm A & B				X	Twice daily dose continuously for 28 days.		X			
Selumetinib Arm C[g]				X	Twice daily - 2 days off prior to (and morning of) each paclitaxel infusion (i.e. day 1-5, 8-12 and 15-26 (evening dose only day 1, 8 and 15)).		X			
Paclitaxel Treatment				X	X	X				
Concomitant Therapy	X			X			X	X		
Adverse Events				X	X[k]	X[k]	X	X[l]		X
Translational Blood	X[i]			X			X	X		
Translational Tissue	X[n]							X[n]		
Collection of FU data									X[m]	
Reason for Discontinuation								X		
Death Form Completed										X

a. Radiological Disease Assessment (RECIST 1.1) at baseline and 8 weekly (± 3 days) calculated from the treatment start date (cycle 1 day 1) until disease progression. All patients will undergo a CT scan of the chest and abdomen. The liver and adrenal glands should be included in the field of view. Any other anatomical sites where disease is suspected or known should also be imaged at baseline. Radiological assessments should be performed using CT scanning; additional liver MRI may be carried out for assessment of liver metastases if measurable disease is not clearly defined on screening CT. If a patient has undergone MRI scan to determine measurable lesions at baseline assessment, they should continue to receive MRI scanning to measure the target lesions. Medical imaging may also be required if a patient deteriorates in-between the tumour assessment (8-weekly) visits. Imaging must always be 8-weekly irrespective of clinic assessment and treatment schedules and should be taken from treatment start date.

b. ECGs should also be conducted as clinically indicated.

c. If it is local practice, bloods may be taken up to 2 days prior so that the results are ready on days 1, 8 and 15 of each cycle.

d. Ophthalmological examination also required if an AE of visual disturbance (including blurring of vision) occurs during treatment with selumetinib. Patients with ongoing retinal abnormality at the time of discontinuation of selumetinib should have a follow-up ophthalmological assessment.

e. LVEF at baseline and every 12 weeks. Assessments to be performed every 12 weeks (±14 days) calculated from the treatment start date (cycle 1 day 1). Assessment times do not shift and continue in accordance with the treatment start date. LVEF required at discontinuation of selumetinib if patients have an ongoing reduction in LVEF of ≥10% & <55%, a single ECG and vital sign assessments should also be conducted 28 days after discontinuation. Either ECHO or MUGA can be used to measure LVEF, but the same technique should be used for all patients at site throughout study.

f. Troponin levels should be measured at baseline and if a clinically significant LVEF reduction (by ≥10% and LLN) or a cardio-respiratory AE of non-obvious occurs during treatment with selumetinib.

g. Arm C - selumetinib to be taken twice daily with 2 days off prior to (and morning of) each paclitaxel infusion (i.e. days 1 to 5, days 8 to 12 and days 15 to 26 of each cycle. Evening dose only on day 1, 8 and 15). And taken continuously after paclitaxel treatment (cycle 7 onwards). For arm C priority should be given to interrupt selumetinib treatment prior to paclitaxel including if the paclitaxel dose is delayed/deferred. Selumetinib dosing has to be interrupted 2/7 before paclitaxel.

h. If screening bloods, ECOG performance status, physical examination and vital signs are within 3 days of starting treatment they can be used for cycle 1, day 1.

i. Baseline translational blood to be collected at screening or pre-treatment cycle 1 - If the translational blood sample is omitted in error at the screening visit, the baseline sample may be taken pre-treatment on cycle 1 day 1 instead.

j. Haematology and Biochemistry bloods are to be collected on day 8 and day 15 of each cycle, prior to paclitaxel treatment for patients on arm B and arm C. Arm A patients (and arm B and C patients who are not receiving paclitaxel) will not be required to have bloods collected on day 8 and day 15 of each cycle. GGT is required at screening and day 1 of each cycle but does not need to be collected on day 8 or day 15.

k. For arm A patients (and arm B and C patients who are not receiving paclitaxel due to paclitaxel treatment being stopped or delayed), adverse event information on day 8 and day 15 can be collected via a phone call to the patient. Arm A patients (and arm B and C patients who are not receiving paclitaxel) will not be required to attend a clinic visit on these days providing AE information is able to be collected.

l. Adverse events should be collected up to 30 days post treatment and any ongoing AE's until end of study.

m. 8-weekly follow-up visits should follow the same schedule as the radiological disease assessment scans for ease of planning. The only follow-up data collected will be 8-weekly (CT ± MRI) scans (RECIST 1.1) for patients that did not show progressive disease at end of treatment or for patients that have progressed, survival data. All AEs should be followed up until satisfactory resolution. If a patient has progressed clinic visits will be as per standard of care until death.

n. FFPE tissue will be collected from the metastatic biopsy and primary ocular tumour (if available) and at progression (optional) refer to section 6.3.

o. Pregnancy testing (for women of child bearing potential only) should be performed at screening and as clinically indicated. For German-patients the international research site will follow the recommendations of the Heads of Medicines Agencies (HMA) working group.

6.3 Translational Substudies

6.3.1. Sample Collection

6.3.1.1. Blood (plasma) Collection

In addition to the patient's routine haematology blood samples, a further 20ml (approx.) of blood (2 x 10 ml) will be taken, at specified time points throughout the study.

These samples will be processed at each trial site, stored at -80°C and then transferred in batches to the GCP Laboratory, University of Liverpool. Samples will then be stored under appropriate conditions for up to 15 years from study start and will be used in future translational studies. The blood samples will be taken prior to the start of treatment and at the start of each cycle. Blood samples for translational work must be taken before the administration of paclitaxel. If a patient is deemed too unwell to receive treatment, every effort should still be made to take the samples.

A separate translational plan will be completed detailing analysis of samples. The SelPac Laboratory Manual will be provided to site on collection procedures and transferring samples to Liverpool before the trial begins at each site.

6.3.1.2. Tissue Samples

The pathways for collecting biopsy samples for translational work are:

1) ***Patient undergoing a diagnostic biopsy*** *(ultrasound or CT-guided)* – This section relates to patients who have not previously undergone a biopsy and but who are being referred for a biopsy procedure and who the research team think would be eligible for the SelPac study if the biopsy were to be confirmative. In this setting the patient should be approached before the diagnostic biopsy to consent to and provide extra biopsy sample(s) for research. This research sample will be taken at the same point as the diagnostic one and will include a Formalin Fixed Paraffin Embedded preparation and should be clearly labelled by the pathology team as for research and transferred to the University of Liverpool. An additional core may also be collected as a fresh frozen sample.

   We ask that patients that are approached to provide research sample(s) at the same time as the diagnostic procedure are done so using the SelPac research biopsy sample PIS and corresponding ICF.

2) ***Collection of surplus tissue*** – Any patient participating in the trial who did not have the extra biopsy at the time of undergoing their diagnostic biopsy, should be approached to see if they will consent to allowing us to use any surplus tissue from the diagnostic biopsy. In addition patients should also be approached to consent to use any stored tissue specimen from their primary cancer of the eye. This information will be provided through the trial specific PIS and ICF.

3) ***Biopsy at the end of treatment*** *(ultrasound or CT-guided)* – If thought to be appropriate patients should be approached for consent for an additional research biopsy at the end of trial treatment (on progression), this should also be done using the SelPac research biopsy sample PIS and corresponding ICF.

6.3.1.3. Chain of Custody

Samples will be transferred from research sites, as per the Laboratory Manual, to the GCP Laboratory Facility at the University of Liverpool. Once transferred they will be under the custodianship of the University of Liverpool as a Human Tissue Authority (HTA) licensed establishment.

Storage Location:
Custodian: Bill Greenhalf - Operational Director Liverpool GCP Facility
Liverpool GCP Labs
1st Floor
William Henry Duncan Building
University of Liverpool
6 West Derby Street
L7 8TX
(note: Please do not ship to this address, this will be provided in the sampling kits)

6.4 Procedures for Assessing Efficacy

Efficacy will be assessed in terms of disease progression and survival (see section 2.3 for details of objectives and section 10.3 for details of outcome measures (endpoints)). The presence of tumour progression will be assessed at 8 week intervals by the PI at each site. Death details will be obtained from the PI at each centre.

6.5 Procedures for Assessing Safety

Safety will be assessed through the reporting of adverse events as described in Section 13. Formal toxicity assessments will be performed at each study visit as described in Section 6. Adverse events will be described using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4, which can be accessed at the following website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40_conversion

6.6 Loss to Follow-Up

If any of the trial patients are lost to follow up, contact will initially be attempted through the PI at each centre. If the PI at the trial centre is not the patient's usual clinician responsible for their speciality care then follow-up will also be attempted through this clinician. Where all of these attempts are unsuccessful, the patient's GP will be asked to provide follow-up information to the recruiting centre.

6.7 Trial Closure

Investigators will be informed when patient recruitment is to cease. Trial enrolment may be stopped at a site when the total requested number of subjects for the trial has been obtained. The ISDMC may recommend to the TSC that the trial be stopped prematurely. Such premature termination/suspension of the trial will be notified to the MHRA and MREC as required.

The end of the trial is defined to be the date on which all patients have been followed up until death **or** until 14 months from the time the last patient has completed trial treatment, if this occurs first.

The trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (IDSMC).

Site and closure activities will be centrally coordinated and conducted in accordance with CTU processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to the applicable ethics and the competent authority.
- Trial-related materials reconciled and returned/disposed of as appropriate
- All site data entered onto the study database, discrepancies raised and satisfactory responses received
- Quality Control checks of the Investigator Site Files, Pharmacy Files and Trial Master File as appropriate.

7 PHARMACOVIGILANCE

7.1 Terms and Definitions

The following definitions have been adapted from European Directive 2001/20/EC and ICH GCP E6.

Adverse Event (AE)
Any untoward medical occurrence (i.e. any unfavourable or unintended sign including abnormal laboratory results, symptom or disease) in a research participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)
Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR)
An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:
a) In the case of a product with a marketing authorization, in the summary of product characteristics for that product
b) In the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)
Any adverse event or adverse reaction is classified as serious if it:

a) results in death
b) is life-threatening* (subject at immediate risk of death)
c) requires in-patient hospitalisation or prolongation of existing hospitalisation**
d) results in persistent or significant disability or incapacity, or
e) consists of a congenital anomaly or birth defect
f) Other important medical events***

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

***Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

7.2 Notes on Adverse Event Inclusions and Exclusions

7.2.1 Include

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment
- Laboratory anomalies that require clinical intervention or further investigation (unless they are associated with an already reported clinical event)
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents

7.2.2 Do Not Include

- Medical or surgical procedures- the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- Overdose of medication without signs or symptoms
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

7.2.3 Reporting of Pregnancy

Pregnancy testing should be conducted prior to study treatment. If a patient or their partner becomes pregnant during treatment, they must be withdrawn immediately.

If a patient or their partner becomes pregnant during treatment or in the six months following treatment, a completed Pregnancy Report Form must be faxed to the LCTC within 24 hours of learning of its occurrence. (Should you need a copy of the Pregnancy Report Form please contact the trial coordinator.) On pregnancy outcome, the final Pregnancy Report Form should be faxed to the LCTC 30 days after the outcome. The final Pregnancy Report Form is used to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy follow-up information on this form also includes an assessment of the possible relationship to the trial medication of any pregnancy outcome. Pregnancy outcomes should also be collected for the female partners of male patient participating in the trial. Consent to report information regarding these pregnancy outcomes should be obtained from the mother prior to completion and faxing of the final Pregnancy Report Form. Any SAE experienced during pregnancy must be reported on the SAE form.

7.3 Notes Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.

Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities
Life threatening
Death

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 7.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

7.4 Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in table 2.
If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigators. In the case of discrepant views on causality between the investigator and others, the MHRA will be informed of both points of view.

Table 2: Definitions of Causality

Relationship	Description
None	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Highly Probable	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

7.5 Expectedness

An AE whose causal relationship to the study drug is assessed by the investigator as "possible", "probable", or "highly probable" is an Adverse Drug Reaction.
All events judged by the investigator to be possibly, probably, or highly probably related to the IMP, graded as serious and **unexpected** for list of Expected Adverse Events (see Reference Safely Information section 7.6) should be reported as a SUSAR.

7.6 Reference Safety Information

The Reference Safety Information (RSI) to be used for this trial is as follows:

- **Selumetinib**: Section 5.4.1 Reference Safety Information for assessment of expectedness of serious adverse events, of the Selumetinib Investigator Brochure.

- **Paclitaxel:** Section 4.8 Undesirable Effects, of the paclitaxel SmPC.
  The paclitaxel brand submitted to the MHRA for Clinical Trials Authorisation is as follows:

  Accord Healthcare Limited Paclitaxel 6 mg/ml Concentrate for Solution for Infusion

7.7 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting SAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

7.8 Reporting Procedures

All new Adverse Events (AEs) that occur either before receiving study medication or 30 days following the last dose of trial treatment do not need to be recorded in the case report form and are not part of the expedited reporting procedure.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

7.8.1 Non Serious ARs/AEs

All such events, whether expected or not, should be recorded in the weekly visit pages of the CRF or, if a field for the event is not provided there, in the AE Form, within 30 days after completion of the final treatment cycle.

7.8.2 Serious ARs/AEs/SUSARs

Investigators **MUST REPORT ALL SERIOUS ADVERSE EVENTS (SAEs),** including disease related as well as treatment related events that occur during and within 30 days following the last dose of trial

treatment. SAEs occurring in patients who have **NOT** received any study treatment do not need to be reported to the sponsor (i.e. patients consented but not yet randomised).

SAEs must be reported within 24 hours of sites becoming aware of them by faxing a completed **SERIOUS ADVERSE EVENT FORM** to the Liverpool Cancer Trials Unit, Fax: **0151 794 8010**.

As an alternative method of reporting (e.g. if fax systems are not working) then a scanned version of the SAE Form may be emailed to the SelPac team. The site must first however contact the specific member of the team to ensure they have access to their emails and are able to accept the scanned SAE.

The SelPac team will acknowledge receipt of the SAE on the same day if sent on a working day between 9am – 5pm or the next working day. If an acknowledgment is not received by site within 2 hours site staff should contact the LCTC.

If all computer and fax systems have failed and an SAE needs to urgently be reported, as a last resort an answer phone message can be left on **0151 794 8935** detailing the SAE.

Blank SAE Forms can be obtained from the CRF library section of the LCTC portal (www.LCTC.org.uk).

Further information for the reporting of German-patient SAEs can be found in the international research site group-specific appendix to the protocol.

Steps for reporting:

i. The SAE form should be completed by the responsible investigator i.e. the consultant named on the 'signature list and delegation of responsibilities log' who is responsible for the patient's care. The investigator should assess the SAE for the likelihood that it is a response to an investigational medicine. In the absence of the responsible investigator the form should be completed and signed by a designated member of the site trial team. The responsible investigator should check the SAE form, make changes as appropriate and sign as soon as possible. The initial report shall be followed by detailed, written reports.
ii. The SAE form should be faxed (or emailed) to the LCTC.
iii. The responsible investigator must notify their R&D department of the event (as per standard local procedure).
iv. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.
v. Follow-up information is noted on the same SAE form. The SAE type check-box at the top of the form should be changed to 'follow-up'. Extra, annotated information and/or copies of test results may be provided separately.
vi. The patient must be identified by trial number, date of birth and initials only. The patient's name should not be used on any correspondence.

The minimum dataset required for a preliminary report should include the following.

- Research subject trial number and initials.
- Date of onset of event.
- Brief description of event and CTCAE (v4) grade.
- Causality relationship.
- Dated signature of investigator/co-investigator and clearly printed name. Date of last administration of study drug.

- Causality relationship.
- Dated signature of investigator/co-investigator and clearly printed name.

PLEASE ENSURE THAT MULITPLE SERIOUS ADVERSE EVENTS ARE REPORTED SEPARATELY TO THE LCTC. ONE SAE REPORT SHOULD ONLY RELATE TO ONE OVERALL DIAGNOSIS.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

The Chief Investigator and the Liverpool Clinical Trials Centre will ensure that all SUSARs are reported to the Sponsor, Competent Authorities (MHRA Clinical Trials Unit) and Ethical Committees within the following timelines.

- Fatal or life threatening SUSARs within 7 days after receiving the initial information.
- All other SUSARs with 15 days after receiving the information.

The Chief Investigator and the Liverpool Clinical Trials Centre will inform all investigators of SUSARs as they occur.

All SUSARs are managed in accordance with the LCTC Pharmacovigilance SOPs and the SelPac Pharmacovigilance plan.

Annual Reporting to MHRA and REC

The sponsor will submit a Development Safety Update Report (DSUR).

The DSUR will present a comprehensive annual review and evaluation of pertinent safety information collected during the reporting period relating to the Investigational Medicinal Product it will cover the following 4 areas:

(1) Examine whether the information obtained by the sponsor during the reporting period is in accordance with previous knowledge of the investigational drug's safety.
(2) Describe new safety issues that could have an impact on the protection of clinical trial subjects.
(3) Summarise the current understanding and management of identified and potential risks.
(4) Provide an update on the status of the clinical investigation/development programme and study results.

7.9 Responsibilities – Investigator

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study product.
All SAEs must be reported immediately by the investigator to the LCTC on an SAE form unless the SAE is specified in the protocol, IB or SmPC as not requiring immediate reporting. All other adverse events should be reported on the regular progress/follow-up reports.

7.10 Responsibilities – LCTC

The LCTC is undertaking duties delegated by the trial sponsor, the University of Liverpool and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA, competent authorities of other European member states in which the trial is taking place and, if required, the research ethics committees) as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the LCTC is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the LCTC first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:
    a. A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial;
    b. A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
    c. A major safety finding from a newly completed animal study (such as carcinogenicity).
    d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;
- Recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the subjects.

Staff at the LCTC will liaise with the designated Clinical Co-ordinator who will evaluate all SAEs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported to regulatory authorities and MREC. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

The LCTC will also send an annual safety report containing a list of all SARs to regulatory authorities and the ethics committee.

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

8 SELECTION OF CENTRES/CLINICIANS

Each participating Centre (and Principal Investigator - PI) has been identified on the basis of:

- Having at least one lead clinician with a specific interest in, and responsibility for, supervising and managing patients with metastatic uveal melanoma.
- Showing enthusiasm to participate in the study.
- Ensuring that sufficient time, staff and adequate facilities are available for the trial.
- Providing information to all supporting staff members involved with the trial or with other elements of the patient's management.
- Acknowledging and agreeing to conform to the administrative and ethical requirements and responsibilities of the study, including signing up to Good Clinical Practice (GCP) and other regulatory documentation.

8.1 Centre/Clinician Inclusion Criteria

a. Positive Site Specific Assessment (SSA) and Local R&D approval through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP)
b. Signed Research Site Agreement (RSA)
c. Completion and return of signature and delegation log to LCTC
d. Curriculum Vitae (CV) including a record of International Conference for Harmonisation (ICH) of GCP training – Principal Investigator (PI)
e. CV (including a record of ICH GCP training) – for each person listed on the on the signature delegation log
f. Clinical Study Protocol Receipt Form
g. Investigator Brochure (IB) & Summary of Product Characteristics (SmPC) Receipt Form
h. Local laboratory accreditation/Quality Check
i. Local laboratory reference ranges
j. Patient Information Sheet (PIS), Informed Consent Form (ICF)and GP letter on trust headed paper
k. Ability to recruit required number of patients (approx. 6 per year)

8.2 Centre/Clinician Exclusion Criteria

Those centres that do not fulfil the above inclusion criteria will not be permitted to participate in the trial.

8.3 Participant Identification Centres (PICs)

The use of PICs for the study is permitted. All participant identification centres must be registered with the LCTC and confirm capacity and capability via the HRA Approvals process.

PIC activity is limited to the following:

- Identification of participants, largely (but not exclusively) through patient records, for possible participation into the study.
- Provide information about/or informs patients directly about the study, e.g. a clinician speaks directly to a patient.

- Advertises the opportunities to participate in the study, e.g. via posters in waiting rooms and where the research is taking place elsewhere.

An organisation is not acting as a PIC when it is responsible for:

- Any protocol-specified assessment to determine participant eligibility for a study, e.g. a screening blood test or x-ray.
- The recruitment (informed consent) of participants into a research study.
- The delivery of research procedures specified in the research protocol.

PIC activity for NHS organisations in England may only commence once HRA Approval has been issued and the instructions regarding the necessity or otherwise of the organisation acting as a PIC and the research site to confirm their capacity and capability to take part has been followed.

PIC activity for organisations in Northern Ireland, Scotland and Wales may only commence once NHS permission is granted by both the research site and the organisation acting as a PIC.

9 TRIAL DESIGN

9.1 Overall Design

A multicentre, phase II, three-arm, randomised parallel group trial.

10 STATISTICAL CONSIDERATIONS

10.1 Introduction

A full and detailed statistical analysis plan will be written and approved prior to final data lock and conduct of the final analysis, in accordance with the LCTC Statistical Analysis and Reporting SOP. Only the main features of these planned statistical analyses (to be performed using a suitable recognised statistical software such as Stata v15 or above, R version 3.2.0 or above and SAS version 9.2 or above) are included here in the main protocol.

10.2 Method of Randomisation

The randomisation code list will be generated by the LCTC trial statistician with the software package Stata using unstratified block randomisation with equal allocation to the three treatment arms.

10.3 Outcome Measures

10.3.1 Primary

Progression-free survival measured from date of randomisation to date of progressive disease or date of death (whichever occurs first).

Patients still alive with no evidence of progression at the time of their most recent visit will be censored at the time of that visit.

10.3.2 Secondary

- Overall survival: will be measured from date of randomisation to the date of death from any cause. Patients still alive at the time of the analysis are censored at the trial cut-off date if known to be alive at this point, (e.g. through subsequent visit) or date of the most recent follow-up otherwise.
- Objective response: is defined as occurrence of complete (CR) or partial responders (PR) as defined by the RECIST version 1.1.
- Toxicity: AEs recorded following randomisation will be classified using the NCI CTCAE version 4.

10.3.3 Exploratory

Translational:

- GNAQ/GNA11 mutation status
- MEK genomic signature

10.4 Sample Size

Based on the results of Carvajal et al (2014), the progression-free survival in the Selumetinib arm is assumed to follow a Weibull distribution with 50% PFS at 3.7 months and 22.9% PFS at 6 months, corresponding to a shape parameter = 1.56 and scale parameter = 4.68.

The estimated recruitment rate/site is based on the actual recruitment rate/site observed in the sites participating in the present study, giving a figure of 0.2 patients/month/site.
The sample size justification is based on comparison of the pooled Paclitaxel arms against the Selumetinib only arm (i.e. a 2:1 allocation ratio) to detect a hazard ratio of 0.55 with a 1-sided 5% significance and 80% power, corresponding to an increase in median progression-free survival from 3.7 months to 5.4 months assuming proportional hazards and Weibull survival distribution as specified above. For this, 68 events will be needed (Stata command *stpower logrank, hratio(0.55) nratio(2) power(0.8) alpha(0.05) onesided*).

In practice, based on recruitment to date and assuming 0.2 patients/month/site the required number of events will be obtained from a total sample size of 72 patients, corresponding to an overall trial duration of 42 months (excluding setup and closedown).

10.5 Interim Monitoring and Analyses

An initial analysis of trial data for ISDMC review is planned at 6 months after the first patient is randomised, to assess recruitment rates and toxicity. The ISDMC will decide on the frequency of subsequent meetings, which must take place at least annually.

There is no stopping rule for efficacy.

This analysis will be undertaken by the SelPac trial statistician at the LCTC. The ISDMC will be asked to consider recruitment rates and toxicity together with results from other relevant trials when reaching any decision regarding early stopping.

10.6 Outline of Analysis

Provided the trial has not been stopped early, the trial statistical analysis will be triggered when 68 progressions have been observed or 7 months after the last patient has been randomised whichever is earlier.

The study will be analysed and reported using the Consolidated Standard of Reporting Trials (CONSORT).

Patient Groups for Analysis
These are defined as follows:

Full Analysis set: In order to follow the Intention to Treat (ITT) principle this will consist of all randomised patients with assessment of the primary outcome excepting for a) patients withdrawing consent between randomisation and starting therapy b) patients withdrawn from the study after randomisation because of irregularities with the consent process and c) patients whose information determining ineligibility existed before randomisation but was not read until after randomisation. Mis-randomised patients will be analysed as randomised.

Per protocol (PP) set: This will consist of those patients in Full Analysis set without any major protocol deviations and who have not withdrawn due to unacceptable toxicity.

Safety set: All patients who received any trial treatment.

Major deviations from protocol that lead to exclusion of a subject from the per-protocol set will be assessed by blind review in cooperation with the Sponsor before data lock.

Efficacy analyses will be performed on the full analysis set and the per protocol set. Safety summaries will be performed on the safety set.

Assessment of study quality & Exposure to treatment/compliance

Study quality will be summarised by treatment arm in terms of withdrawals/losses to follow-up, frequency of deviations, and extent of missing critical data.

Exposure to treatment will be compared across treatment arms by calculating the mean percentage of cycles with delayed, reduced and omitted doses.

Description of baseline subject characteristics

Continuous variables will be summarised, provided they follow approximate normality, using the mean and standard deviation. If this is not the case, then the median, IQR and range will be provided. Categorical data will be summarised in terms of frequency (n) and percentage, presented by treatment arm. All data will be presented by treatment arm.

Levels of significance, width of confidence intervals

Significance levels will be 5% one-sided for, comparing PFS in the combined Paclitaxel arms to the selumetinib arm. Estimates will be presented with 90% confidence intervals (consistent with the one-sided 5% significance for PFS). No adjustment will be made for multiple comparisons.

Analysis of primary and secondary outcomes

The primary test of efficacy in terms of progression-free survival will be carried out on an Intention to Treat basis using a log rank test. Estimation of the treatment effect (as a hazard ratio) will be obtained using a Cox proportional hazards model. Kaplan-Meier survival plots will be displayed for progression free survival split by treatment arm. The graph will show the results of the log rank test in addition to the median event time and estimated hazard ratio (displayed with their respective confidence intervals). The same procedure will be used to analyse overall survival as a secondary outcome.

Secondary analysis on the primary outcome will separately compare each Paclitaxel arm with the continuous Selumetinib arm. The methodology will replicate that of the primary analysis. This will be undertaken to investigate any differences in treatment effect which may be attributable to the mode of administration.

Sensitivity analyses analysis will use the per protocol population to demonstrate robustness of the results to unsatisfactory compliance. Further sensitivity and secondary outcome analyses are detailed in the Statistical Analysis report.

Analysis of safety & tolerability

Adverse events (AEs) will be categorised using the NCI CTCAE, Version 4. The number and percentage of patients reporting a Serious Adverse Event (SAE) and Grade 3 or higher toxicity that led to study discontinuation will be summarised by treatment arm and preferred term (if severity is missing, the worst case will be assumed).

The number and proportion of patients experiencing an SAE or toxicity by grade will be tabulated across treatment arms. The frequencies in the combined Paclitaxel arm and Selumetinib arm will be compared using 'exact' methods. Comparisons will use conventional two-sided 95% confidence intervals and 5% two-sided significance. If indicated by the pattern of SAEs or SARs or efficacy, the two Paclitaxel arms may be analysed separately.

Prespecified subgroup analyses

None specified as yet; all will require prior justification and kept to a minimum. Further details will be included in a formal Statistical Analysis Plan, to be signed off before data lock.

10.7 Translational Studies

Planned subgroup analyses will be performed to explore the effects of GNAQ/GNA11 mutation status and MEK signature by fitting Cox proportional hazards regression models for the outcomes PFS and OS, and logistic regression models for the response outcome, with testing for main effect to indicate prognostic importance, and testing for treatment by marker interaction to assess predictive value, with allowance for Helsinki stage and baseline LDH. Again, conventional two-sided 95% confidence intervals and 5% two-sided significance will be used. Samples will be stored in a tissue bank and will be made available for future biomarker studies. These will have a separate protocol and SAP.

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

The SelPac trial will be conducted in accordance with, but not limited to, the Human Rights Act 1998, the DPA, Freedom of Information Act 2000 subject to the provisions of sections 41 and 43 thereof, the EU Clinical Trials Directive, the Medicines for Human Use (Clinical Trials) Regulations 2004, the Medicines Act 1968, the Human Tissue Act 2004, ICH GCP, the Declaration of Helsinki 1996 and the NHS Research Governance Framework for Health and Social Care, as amended from time to time. Patients will be asked to consent that data are recorded, collected, stored and processed and may be transferred to other countries, in accordance with any national legislation implementing the EU Data Protection Directive (95/46/EC).

Patients will be asked to consent that data are recorded, collected, stored and processed and may be transferred to other countries, in accordance with any national legislation implementing the EU Data Protection Directive (95/46/EC) and to allow a copy of their completed signed consent form to be sent to the Liverpool Cancer Trials Unit.
This study may be terminated at the request of the CI, ISDMC, independent Research Ethics Committee (REC) or the MHRA if, during the course of the study, concerns about the safety of further dosing emerge.

The CI will update the ethics committee of any new information related to the study drug when appropriate and this will also be disseminated to the Principal Investigators at each trial centre.

11.2 Ethical Approval

The trial protocol has received the favourable opinion of the London City & East Multi-centre Research Ethics Committee (MREC) but all participating sites must undergo site specific assessment via the IRAS (Integrated Research Application System). A copy of all site approval documents and a copy of the PIS and ICF on local headed paper should be forwarded to LCTC before patients are entered. The LCTC should receive notification of positive SSA for each new centre via the site's R&D department.

11.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all patients participating in LCTC coordinated trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to patients by staff with appropriate experience. An appropriate Patient Information and Consent forms, describing in detail the trial interventions/products, trial procedures and risks will be approved by an independent ethical committee (IEC) and the patient will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the patient and answer any questions that may arise. A contact point where further information about the trial may be obtained will be provided.

After being given adequate time to consider the information, the patient will be asked to sign the informed consent document. A copy of the informed consent document will be given to the patient for their records and a copy placed in the medical records, with the original retained in the Investigator Site File.

After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the patient remains free to withdraw at any time from the protocol treatment and trial follow-up by without giving reasons and without prejudicing the further treatment. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

Patients may withdraw from the trial at any time by revoking the informed consent.

All patients will continue to be followed for survival in all cases other than those who withdraw consent.

11.4 Study Discontinuation

The reason for discontinuation of study treatment/study should be clearly documented and the end of treatment and end of study CRFs completed.

12 REGULATORY APPROVAL

This trial has been registered with the MHRA and has been granted a Clinical Trial Authorisation (CTA). The CTA reference is EudraCT Number: 2014-004437-22.

13 TRIAL MONITORING

Central and site monitoring is conducted to ensure protection of patients participating in the trial, and that trial procedures, trial intervention administration, and laboratory and data collection processes are of high quality and meet sponsor and, when appropriate, regulatory requirements. A risk assessment will be carried out to determine the level of monitoring required, and a subsequent monitoring plan will be developed to document who will conduct the central (and potentially site) monitoring, at what frequency monitoring will be carried out and the level of detail at which monitoring will be conducted.

13.1 Risk Assessment

In accordance with the LCTC SOPs a risk assessment has been completed in partnership with:

- Representatives of the Trial Sponsors
- Chief Investigator
- Trial Coordinator
- Trial Statistician
- LCTC Operational Director

In conducting this risk assessment, the contributors considered potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur.

The outcome of the risk assessment is categorised into three groups:

CTIMP Type A = Comparable to the risk of standard medical care.
CTIMP Type B = Somewhat higher than the risk of standard medical care.
CTIMP Type C = Markedly higher than the risk of standard medical care.

The risk assessment resulted in this trial being categorised as a type C CTIMP, as selumetinib has previously been used in clinical trials, for which safety is available, however there is no market authorisation for this drug.

13.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy and laboratory departments involved in the clinical trial.

13.3 Data Capture Methods

Trial data will be captured using paper case report forms.

13.3.1 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

CRF pages will be available for sites to download from the LCTC portal: http://www.LCTC.org.uk

13.4 Monitoring at LCTC

There are a number of monitoring features in place at the LCTC to ensure reliability and validity of the trial data.

13.4.1 Green Light Process

The Green Light Process in place at the LCTC means that no patients can be randomised at a particular site without the green light being given. It ensures that all approvals must be in place, all contracts/agreements signed and all trial-specific and ICH GCP training received by site research staff before patients can enter the trial.

13.4.2 Site Research Staff

All site research staff involved in the trial must be included on the delegation log. The PI at each site signs off on the delegation log only those staff members he/she feels are able and competent to complete the assigned tasks. The delegation log provides clearly defined delegation of responsibility thus ensuring site research staff are aware of their responsibilities, and is continuously checked (as part of the data management plan) against staff named on CRFs, SAE reports and randomisation forms.

The TC ensures that all delegated staff have documented trial-specific training (on the protocol, SAE reporting and consent process) all of which is provided at site initiation (either on site or by teleconference) by the TC and on a continuous basis throughout the trial when new staff are added to the delegation log. Sites are supplied with copies of training aids presented at site initiation to provide a constant reminder of key trial issues. Delegated site research staff must also submit their CV and provide the date of their last ICH GCP training. In order to ensure that site research staff maintain up to date ICH GCP training (to be renewed every 3 years as suggested by ICH GCP), an automated email reminder is sent to site research staff when their next ICH GCP training is due. Non-NHS staff must have honorary contracts and evidence of CRB checks must be obtained for staff (when necessary by UK law).

Automated 6-monthly email reminders (from site opening) are sent to sites requesting that an updated delegation log is faxed to LCTC. On receipt of updated delegation logs, the TC ensures that new staff have submitted their CVs and date of last ICH GCP training, as well as providing them with trial-specific training.

Pharmacy staff must complete drug accountability logs for each patient whenever trial drug is dispensed, and these are checked (as part of the data management plan) against drug administration details (dose, date dispensed, batch number, expiry date and who dispensed each administered treatment) recorded on CRFs by the research nurses. Automated email reminders are sent to pharmacies (after induction, and annually during maintenance, for each patient) requesting that a copy of the drug accountability log is sent to LCTC.

13.4.3 Oversight Committees

The ISDMC is an independent multidisciplinary group consisting of at least one statistician and at least one clinician that, collectively, have experience in the management of oncology and in the conduct of randomised clinical trials. They are responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial and for monitoring the overall progress and conduct of the clinical trial.

The TSC includes an independent Chairman and two additional independent expert members (one being a statistician) and a lay/consumer representative, along with members of the TMG. Among other things, the TSC takes responsibility for monitoring and supervising the progress of the trial, considering recommendations from the ISDMC and advising the TMG on all aspects of the trial.

13.4.4 Safety Reports

Monthly safety reports are generated by the TC which allows monitoring of SAE and ADR reporting rates across sites. The ISDMC also regularly review AE and SAE reporting, and the TC prepares Annual Safety Reports for submission to the MHRA and REC. Any concerns raised by the ISDMC or inconsistencies noted at a given site may prompt additional training at sites, with the potential for the TC to carry out site visits if there is suspicion of unreported AEs in patient case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines (as outlined in the pharmacovigilance plan) is noted at a given site.

13.4.5 Randomisation

The TC verifies that all site research staff have attended trial-specific training relating to eligibility screening and the informed consent/randomisation process. Prior to randomisation, the TC/Data Manager (DM) carry out a check of all consent forms sent to the LCTC. This includes checking that the patient is eligible, the correct versions of the Patient Information Sheet (PIS) and Patient Informed Consent (PIC) Forms have been used, and the patient and clinician signatures are present and dated on the same day. Automated 6-monthly email reminders (from site opening) are sent to sites requesting that they fax a copy of the screening log to the LCTC. On receipt of this screening log, the DM carries out a check of all randomised patients to ensure that at least 24 hours lapsed between the informed consent discussion and randomisation.

13.4.6 Patient Confidentiality

All LCTC and site research staff have received ICH GCP training and are thus aware of the importance of patient confidentiality. The TC/DM consistently check that the CRFs sent to LCTC are all anonymised and are identifiable only by trial number (except for signed consent forms, which are stored in a locked cabinet in the LCTC). The TC will monitor site performance on maintaining patient confidentiality and

will provide additional training if a particular site sends any patient identifiers to LCTC (other than on the signed consent form).

13.4.7 Recruitment

The TC will produce monthly recruitment reports, to allow the ISDMC, TSC and TMG to regularly review recruitment across sites. Slow or inconsistent recruitment will trigger further action centrally. The TC may liaise directly with site staff in order to query reasons for slow recruitment and try to resolve any problems that could impact recruitment. TC will check that the trial is being actively promoted at sites, and site recruitment schedules will be reviewed during the course of the trial as necessary.

13.4.8 Protocol Violations/Deviations

All protocol violations and deviations are recorded by the TC in the trial site status database, and are included in the regular ISDMC reports. The TC sends details of all protocol violations and deviations to the CI as soon as the LCTC is made aware of such occurrences, and any that are considered to be a potential serious breach would be forwarded immediately to the Sponsor. Details of all other protocol violations and deviations are sent to the Sponsor on a monthly basis for their review. If it is noted that a particular site is making consistent protocol violations or deviations, additional training will be provided by the TC. Deviations that will have a serious impact on the statistical analysis such as missing primary endpoint, stratification variables or preplanned covariates, or where extent of treatment is deemed inadequate to produce a therapeutic effect are by definition major and must be flagged so that the patient can be excluded from the per-protocol analysis.

13.4.9 Withdrawals, Losses to Follow Up and Missing Data

The TC will produce reports on withdrawals, losses to follow-up and the quantity of missing CRFs/data across sites for review by the LCTC business meeting, TMG, TSC and ISDMC. Identified problems will be discussed and remedial action taken as necessary.

As outlined in the data management plan, the TC/DM will check that the withdrawal CRF is completed for all withdrawn patients (including the reasons for withdrawal). The TC will compare withdrawal rates and reasons for withdrawal across centres, paying particular attention to withdrawals close to date of randomisation. If a certain site experiences an excessive rate of withdrawals, additional training on the informed consent procedure will be provided.

13.4.10 Data Management Plan

CRF data entered into the MACRO database will be centrally monitored by the LCTC to ensure that data collected are consistent with adherence to the trial protocol. The MACRO database used for this trial includes validation features which will alert the user to certain inconsistent or missing data on data entry. If any problems are identified via automated validation or central monitoring, a query is raised within the MACRO database and emailed to site. A complete log of discrepancies and data amendments is automatically generated by MACRO, including the date of each change, the reason for the change and the person who made the change, thus providing a complete audit trail. Automated email reminders are generated by the database if follow up data from a scheduled patient visit is overdue.

Additional site training will be carried out if recurring problems are noted with data from a certain site, such as consistently incorrect or incomplete data, a backlog of unresolved queries, or unacceptable time delays in submitting CRFs.

13.4.11 Statistical Monitoring

Limited central statistical monitoring is carried out by the trial statistician prior to the production of each ISDMC report. The statistician checks trial numbers to ensure there are no duplicated or missing numbers, and that randomisation dates for consecutive trial numbers are in the correct order.

Eligibility criteria and informed consent are checked to ensure all are documented and satisfied by the TC and DM. Monitoring is used to highlight suspicions of fraudulent data (by carrying out range checks for unusual values, checking for consistency within participants and comparing data across sites to highlight inconsistencies), as well as providing a record of the degree of missing CRFs and follow up visits, and missing baseline and outcome data. Safety and withdrawal data are also reviewed for completeness by the TC and DM.

If there is compelling evidence to suggest that data from a particular site may be fraudulent, the TC may request a site visit to carry out source document verification of patient case notes and other source documentation.

13.4.12 LCTC Staff

All LCTC staff will receive regular ICH GCP training, have in-house training records and undergo regular Individual Performance Review (IPR) sessions, all of which are used to ensure that appropriate training is received and any problems identified and resolved in a timely fashion.

13.5 Clinical Site Monitoring

13.5.1 Direct Access to Data

In order to perform their role effectively, monitors and persons involved in Quality Assurance and Inspection will need direct access to primary subject data, e.g. patient records, laboratory reports, appointment books, etc. Because this affects the patient's confidentiality, this fact is included on the Patient Information Sheet and Informed Consent Form.

13.5.2 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Case report forms will be labelled with patient initials and unique trial screening and/or trial number. Blood samples and paraffin blocks will be transferred to the Liverpool Experimental Cancer Medicine Centre GCP Laboratory and will be identifiable by unique trial number only. Consent forms sent to the LCTC as part of the randomisation process may contain patient identifiers for the purpose of monitoring as described in the trial risk assessment. Such information will be stored in secure, locked cabinets.

The LCTC will request consent from all patients to obtain information from the NHS Information Centre (Medical Research Information Service).

13.5.3 Quality Assurance and Quality Control of Data

Systems of quality assurance, including all elements described in this protocol have been/will be implemented within relevant institutions with responsibility for this trial. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

The SelPac Investigational sites, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit and inspection by competent or IEC. Such audits/inspections may take place at any site where trial related activity is taking place (the Sponsors site(s), Cancer Research UK (CR-UK) Liverpool Clinical Trials Centre or at any investigators site including laboratories, pharmacies etc).

The site staff should assist in all aspects of audit/inspection and be fully cognisant of the LCTC communication strategy for multicentre trials. This includes management systems for the GREEN light process prior to drug release to site, conforming to the total Quality Management System currently operating within the LCTC.

13.6 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Trial File, until the LCTC informs the investigator that the documents are no longer to be retained.

In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities). The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The LCTC undertakes to store originally completed CRFs and separate copies of the above documents for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only.

Essential documents should be retained until at least 2 years after last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Product. These documents should be retained for a longer period however if required by applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Verification of appropriate informed consent will be enabled by the provision of copies of participants' signed informed consent/assent forms being supplied to the LCTC by recruiting centres. This requires that name data will be transferred to the LCTC, which is explained in the PISC. The LCTC will preserve the confidentiality of participants taking part in the study and the University of Liverpool is a Data Controller registered with the Information Commissioners Office.

14 INDEMNITY

SelPac is sponsored by the University of Liverpool and co-ordinated by the LCTC in the University of Liverpool. The University of Liverpool does not hold insurance against claims for compensation for injury caused by participation in a clinical trial. However the University of Liverpool does hold appropriate insurance for the design of the trial i.e. if the injury is as a result of the management or design of the study, and all procedures conducted at site are in line with the protocol. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

15 FINANCIAL ARRANGEMENTS

This is a non-commercial trial, and no direct payments are available to cover the costs associated with patient recruitment, treatment administration, follow-up visits, data collection or reasonable travel expenses. The trial is part of the NCRN and AstraZeneca collaboration portfolio and is endorsed by Cancer Research UK, consequently having automatic endorsement from the National Cancer Research Network (NCRN) and UK Clinical Research Network (UKCRN). These organisations will be responsible for providing local investigators with the necessary research infrastructure. Selumetinib will be provided free of charge by AstraZeneca.

16 TRIAL OVERSIGHT COMMITTEES

16.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the Liverpool Clinical Trials Unit. The TMG will be responsible for the day-to-day running and management of the trial and will meet approximately 3 times a year.

16.2 Trial Steering Committee (TSC)

The Trial Steering Committee will consist of an independent chairperson, 2 independent experts in the field of uveal melanoma and a biostatistician and up to seven Principal Investigators. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.

16.3 Independent Safety and Data Monitoring Committee (ISDMC)

The Independent Safety and Data Monitoring Committee (ISDMC) consist of an independent chairperson, plus 2 independent members, one of whom is an expert in the field of uveal melanoma and an expert in medical statistics.

The ISDMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The ISDMC will first convene before the trial starts at which the frequency of subsequent meetings (at least annually) will be defined. An ISDMC is also planned 6 months after the first patient is randomised. Details of the interim analysis and monitoring are provided in section 10.

The ISDMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the study.

17 PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and ISDMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

18 PROTOCOL AMENDMENTS

Version	Summary of Changes
Protocol Version: 1 Date: 16-Dec-2014	Original submitted for approval.
Protocol Version: 2 Date: 20-Mar-2015	Original approved version, with updates as requested by the competent authority.
Protocol Version: 3 Date: 20-Jul-2016	a. Addition of ISRCTN and EudraCT number and update to trial contact details. b. Update to UK Registration statement to document the HRA Approval process. c. Update to trial background to include SUMIT study findings. d. Inclusion criteria: change in reporting units for haemoglobin and creatinine. e. Exclusion criteria: point 2 and point 6 consolidated to avoid repetition i.e. leptomeningeal metastases added to list in point 2 - exclusion for patients who have a known or suspected brain or leptomeningeal metastases, or spinal cord compression, unless asymptomatic. f. Exclusion criteria: point 11, update to wording, effective methods of contraception rather than method. g. Clarification for arm C dosing schedule, selumetinib is to be omitted 2 days prior to (and the morning of) each paclitaxel infusion. h. Addition of information for the preparation of paclitaxel. i. Addition of information for the continued provision of selumetinib. j. Addition of liver MRI as a technique for radiological disease assessment. k. Scan and LVEF assessment times to be performed from the treatment start date. l. Update to the schedule of procedures for clarification only; to clarify screening assessment timeframes, visits for arm A patients, visits and procedures for cycle 7 onwards (continuous selumetinib) and the allowed window for 8 weekly (±3 days) scans and 12 weekly (±14 days) LVEF assessments. m. Medical history review to be carried out at screening & baseline only. n. If a patient has progressed clinic visits will be as per standard of care until death. o. Biopsy procedures to be performed under ultrasound or CT-guidance. p. Update to contraception advice; two reliable methods of contraception required. q. Addition of the use of participant identification centres for the SelPac study. r. Updates to statistical considerations with more detail about planned analyses. s. Update to the statement of indemnity, UoL holds appropriate insurance for the design of the trial. t. Miscellaneous administrative and formatting changes.
Protocol Version: 4 Date: 24-Jan-2018	a. Addition of sponsor protocol reference number and update to trial contact details, including named trial statistician. b. Further detail on the rationale for IMP doses provided. c. Retinal vein occlusion added to the list of identified risks with selumetinib use. d. Inclusion criteria: point 7, updated to consider endocrinopathies treated with hormone replacement. e. Inclusion criteria: point 10, requirement for written informed consent added for clarification. f. Exclusion criteria: point 5 updated, statement concerning toxicities from previous treatments removed as this is defined in the inclusion criteria. g. Exclusion criteria: point 7 updated, caveat added for hypertension criteria concerning German-patients only. h. Exclusion criteria: point 12 added, German-patients who are placed on administrative order in an institution or are dependant from the sponsor or study doctor are excluded from the study. i. Further clarification on follow up visit schedule provided. j. Pregnancy test information updated, urine or serum testing is permitted.

	k. Biochemistry information updated, GGT test is not required on day 8 and 15 of each cycle. Phosphate test added. l. Clarification provided on arm B and C selumetinib dosing following paclitaxel discontinuation. m. Update to selumetinib specific restrictions advice for consistency with the main trial PIS. Patients should avoid consuming grapefruits, Seville oranges, or any other products that may contain these fruits. n. Update to the schedule of procedures for clarification only; to clarify end of treatment, follow-up and end of study visit timeframes. o. Pregnancy testing (for women of child bearing potential only) should be performed at screening and as clinically indicated. p. SAE reporting instructions for site, wording updated for clarity. q. Miscellaneous administrative and formatting changes.
Protocol Version: 5 Date: 04-Jul-2018	a. Update to the statistical design, planned sample size and overall study duration. b. Update to the primary analysis method (removal of post stratification factors). c. Removal of the futility analysis. d. Wording for translational sample chain of custody added for clarification purposes. e. Miscellaneous administrative and formatting changes.
Protocol Version: 6 Date: 22-Mar-2019	a. Update to the statistical analysis section for clarification purposes; wording updated to allow analyses to be undertaken with statistical software other than Stata, exploratory translational outcomes paragraph separated into a sub-section and wording corrected for final analysis trigger.
Protocol Version: 7 Date: 13-May-2020	a. Contact details updated. b. Paragraph added to provide information on trials unit merger. c. Update to translational sample storage location. d. Update to the wording for LPLV and trial closure. e. Update to statistical section 10.4 for consistency with LPLV statement.

19 REFERENCES

AMBROSINI, G., PRATILAS, C. A., QIN, L. X., TADI, M., SURRIGA, O., CARVAJAL, R. D. & SCHWARTZ, G. K. 2012. Identification of unique MEK-dependent genes in GNAQ mutant uveal melanoma involved in cell growth, tumor cell invasion, and MEK resistance. *Clin Cancer Res,* 18**,** 3552-61.

CARVAJAL, R. D., SOSMAN, J. A., QUEVEDO, J. F., MILHEM, M. M., JOSHUA, A. M., KUDCHADKAR, R. R., LINETTE, G. P., GAJEWSKI, T. F., LUTZKY, J., LAWSON, D. H., LAO, C. D., FLYNN, P. J., ALBERTINI, M. R., SATO, T., LEWIS, K., DOYLE, A., ANCELL, K., PANAGEAS, K. S., BLUTH, M., HEDVAT, C., ERINJERI, J., AMBROSINI, G., MARR, B., ABRAMSON, D. H., DICKSON, M. A., WOLCHOK, J. D., CHAPMAN, P. B. & SCHWARTZ, G. K. 2014. Effect of selumetinib vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial. *Jama,* 311**,** 2397-405.

DAVIES, B. R., LOGIE, A., MCKAY, J. S., MARTIN, P., STEELE, S., JENKINS, R., COCKERILL, M., CARTLIDGE, S. & SMITH, P. D. 2007. AZD6244 (ARRY-142886), a potent inhibitor of mitogen-activated protein kinase/extracellular signal-regulated kinase kinase 1/2 kinases: mechanism of action in vivo, pharmacokinetic/pharmacodynamic relationship, and potential for combination in preclinical models. *Mol Cancer Ther,* 6**,** 2209-19.

DRY, J. R., PAVEY, S., PRATILAS, C. A., HARBRON, C., RUNSWICK, S., HODGSON, D., CHRESTA, C., MCCORMACK, R., BYRNE, N., COCKERILL, M., GRAHAM, A., BERAN, G., CASSIDY, A., HAGGERTY, C., BROWN, H., ELLISON, G., DERING, J., TAYLOR, B. S., STARK, M., BONAZZI, V., RAVISHANKAR, S., PACKER, L., XING, F., SOLIT, D. B., FINN, R. S., ROSEN, N., HAYWARD, N. K., FRENCH, T. & SMITH, P. D. 2010. Transcriptional pathway signatures predict MEK addiction and response to selumetinib (AZD6244). *Cancer Res,* 70**,** 2264-73.

GUPTA, A., LOVE, S., SCHUH, A., SHANYINDE, M., LARKIN, J. M., PLUMMER, R., NATHAN, P. D., DANSON, S., OTTENSMEIER, C. H., LORIGAN, P., COLLINS, L., WISE, A., ASHER, R., LISLE, R. & MIDDLETON, M. R. 2014. DOC-MEK: a double-blind randomized phase II trial of docetaxel with or without selumetinib in wild-type BRAF advanced melanoma. *Ann Oncol,* 25**,** 968-74.

HODI, F. S., O'DAY, S. J., MCDERMOTT, D. F., WEBER, R. W., SOSMAN, J. A., HAANEN, J. B., GONZALEZ, R., ROBERT, C., SCHADENDORF, D., HASSEL, J. C., AKERLEY, W., VAN DEN EERTWEGH, A. J., LUTZKY, J., LORIGAN, P., VAUBEL, J. M., LINETTE, G. P., HOGG, D., OTTENSMEIER, C. H., LEBBÉ, C., PESCHEL, C., QUIRT, I., CLARK, J. I., WOLCHOK, J. D., WEBER, J. S., TIAN, J., YELLIN, M. J., NICHOL, G. M., HOOS, A. & URBA, W. J. 2010. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med,* 363**,** 711-23.

HOLT, S. V., LOGIE, A., ODEDRA, R., HEIER, A., HEATON, S. P., ALFEREZ, D., DAVIES, B. R., WILKINSON, R. W. & SMITH, P. D. 2012. The MEK1/2 inhibitor, selumetinib (AZD6244; ARRY-142886), enhances anti-tumour efficacy when combined with conventional chemotherapeutic agents in human tumour xenograft models. *Br J Cancer,* 106**,** 858-66.

HOMSI, J., BEDIKIAN, A. Y., PAPADOPOULOS, N. E., KIM, K. B., HWU, W. J., MAHONEY, S. L. & HWU, P. 2010. Phase 2 open-label study of weekly docosahexaenoic acid-paclitaxel in patients with metastatic uveal melanoma. *Melanoma Res,* 20**,** 507-10.

JANNE, P. A., SHAW, A. T., PEREIRA, J. R., JEANNIN, G., VANSTEENKISTE, J., BARRIOS, C., FRANKE, F. A., GRINSTED, L., ZAZULINA, V., SMITH, P., SMITH, I. & CRINO, L. 2013. Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study. *Lancet Oncol,* 14**,** 38-47.

KEENAN, T. D., YEATES, D. & GOLDACRE, M. J. 2012. Uveal melanoma in England: trends over time and geographical variation. *Br J Ophthalmol,* 96**,** 1415-9.

KHAN, S., CALLAHAN, M., POSTOW, M., CHAPMAN, P., SCHWARTZ, G., DICKSON, M., D'ANGELO, S., LUKE, J., BLUTH, M., ROMAN, R., MONTEFUSCO, M., BARKER, C., ABRAMSON, D., WOLCHOK, J. & CARVAJAL, R. 2012. Ipilimumab in the treatment of uveal melanoma: The Memorial Sloan-Kettering Cancer Center experience. *J Clin Oncol,* 30.

KIRKWOOD, J. M., BASTHOLT, L., ROBERT, C., SOSMAN, J., LARKIN, J., HERSEY, P., MIDDLETON, M., CANTARINI, M., ZAZULINA, V., KEMSLEY, K. & DUMMER, R. 2012. Phase II, open-label, randomized trial of the MEK1/2 inhibitor selumetinib as monotherapy versus temozolomide in patients with advanced melanoma. *Clin Cancer Res,* 18**,** 555-67.

KUJALA, E., MÄKITIE, T. & KIVELÄ, T. 2003. Very long-term prognosis of patients with malignant uveal melanoma. *Invest Ophthalmol Vis Sci,* 44**,** 4651-9.

LUKE, J. J., TRIOZZI, P. L., MCKENNA, K. C., VAN MEIR, E. G., GERSHENWALD, J. E., BASTIAN, B. C., GUTKIND, J. S., BOWCOCK, A. M., STREICHER, H. Z., PATEL, P. M., SATO, T., SOSSMAN, J. A., SZNOL, M., WELCH, J., THURIN, M., SELIG, S., FLAHERTY, K. T. & CARVAJAL, R. D. 2014. Biology of advanced uveal melanoma and next steps for clinical therapeutics. *Pigment Cell Melanoma Res*.

MACKEIGAN, J. P., COLLINS, T. S. & TING, J. P. 2000. MEK inhibition enhances paclitaxel-induced tumor apoptosis. *J Biol Chem,* 275**,** 38953-6.

MCDAID, H. M., LOPEZ-BARCONS, L., GROSSMAN, A., LIA, M., KELLER, S., PEREZ-SOLER, R. & HORWITZ, S. B. 2005. Enhancement of the therapeutic efficacy of taxol by the mitogen-activated protein kinase kinase inhibitor CI-1040 in nude mice bearing human heterotransplants. *Cancer Res,* 65**,** 2854-60.

ONKEN, M. D., WORLEY, L. A., LONG, M. D., DUAN, S., COUNCIL, M. L., BOWCOCK, A. M. & HARBOUR, J. W. 2008. Oncogenic mutations in GNAQ occur early in uveal melanoma. *Invest Ophthalmol Vis Sci,* 49**,** 5230-4.

ROBERT, C., DUMMER, R., GUTZMER, R., LORIGAN, P., KIM, K. B., NYAKAS, M., ARANCE, A., LISZKAY, G., SCHADENDORF, D., CANTARINI, M., SPENCER, S. & MIDDLETON, M. R. 2013. Selumetinib plus dacarbazine versus placebo plus dacarbazine as first-line treatment for BRAF-mutant metastatic melanoma: a phase 2 double-blind randomised study. *Lancet Oncol,* 14**,** 733-40.

SACCO, J. J., NATHAN, P. D., DANSON, S., LORIGAN, P., NICHOLSON, S., OTTENSMEIER, C., CORRIE, P., STEVEN, N., GOODMAN, A., LARKIN, J., EVANS, T. R. J., KUMAR, S., COUPLAND, S. E., SILCOCKS, P. & MARSHALL, E. 2013. Sunitinib versus dacarbazine as first-line treatment in patients with metastatic uveal melanoma. *J Clin Oncol,* 31**,** suppl; abstr 9031.

TAXMAN, D. J., MACKEIGAN, J. P., CLEMENTS, C., BERGSTRALH, D. T. & TING, J. P. 2003. Transcriptional profiling of targets for combination therapy of lung carcinoma with paclitaxel and mitogen-activated protein/extracellular signal-regulated kinase kinase inhibitor. *Cancer Res,* 63**,** 5095-104.

VAN RAAMSDONK, C. D., GRIEWANK, K. G., CROSBY, M. B., GARRIDO, M. C., VEMULA, S., WIESNER, T., OBENAUF, A. C., WACKERNAGEL, W., GREEN, G., BOUVIER, N., SOZEN, M. M., BAIMUKANOVA, G., ROY, R., HEGUY, A., DOLGALEV, I., KHANIN, R., BUSAM, K., SPEICHER, M. R., O'BRIEN, J. & BASTIAN, B. C. 2010. Mutations in GNA11 in uveal melanoma. *N Engl J Med,* 363**,** 2191-9.

WALLACE, E., YEH, T., LYSSIKATOS, J., WINKLER, J., LEE, P., MARLOW, A., HURLEY, B., MARSH, V., BERNAT, B., EVANS, R., COLWELL, H., BALLARD, J., MORALES, T., SMITH, D., BRANDHUBER, B., GROSS, S., POCH, G., LITWILER, K., HINGORANI, G., OTTEN, J., SULLIVAN, F., BLAKE, J., PHENEGER, T., GOYETTE, M. & KOCH, K. 2004. Preclinical development of ARRY-142886, a potent and selective MEK inhibitor. *AACR Meeting Abstracts,* 2004**,** 897-a-.

XU, R., SATO, N., YANAI, K., AKIYOSHI, T., NAGAI, S., WADA, J., KOGA, K., MIBU, R., NAKAMURA, M. & KATANO, M. 2009. Enhancement of paclitaxel-induced apoptosis by inhibition of mitogen-activated protein kinase pathway in colon cancer cells. *Anticancer Res,* 29**,** 261-70.

20 APPENDICES

Appendix 1:

New York Heart Association (NYHA) classification of heart disease

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while **at rest**. Mostly bedbound patients.

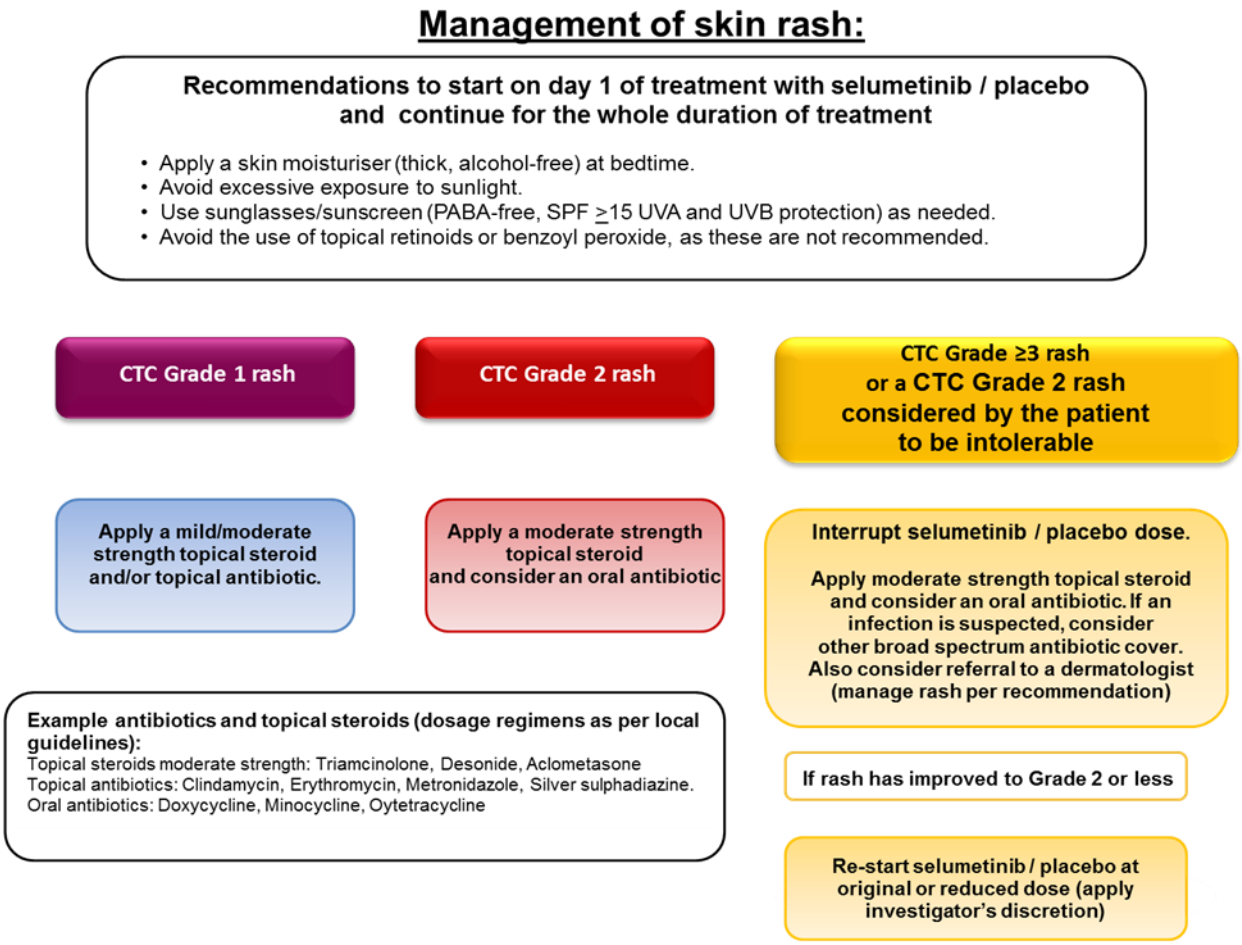
Appendix 2:

Canadian Cardiovascular Society grading of angina pectoris

Grade	Description
I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions
III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace
IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest

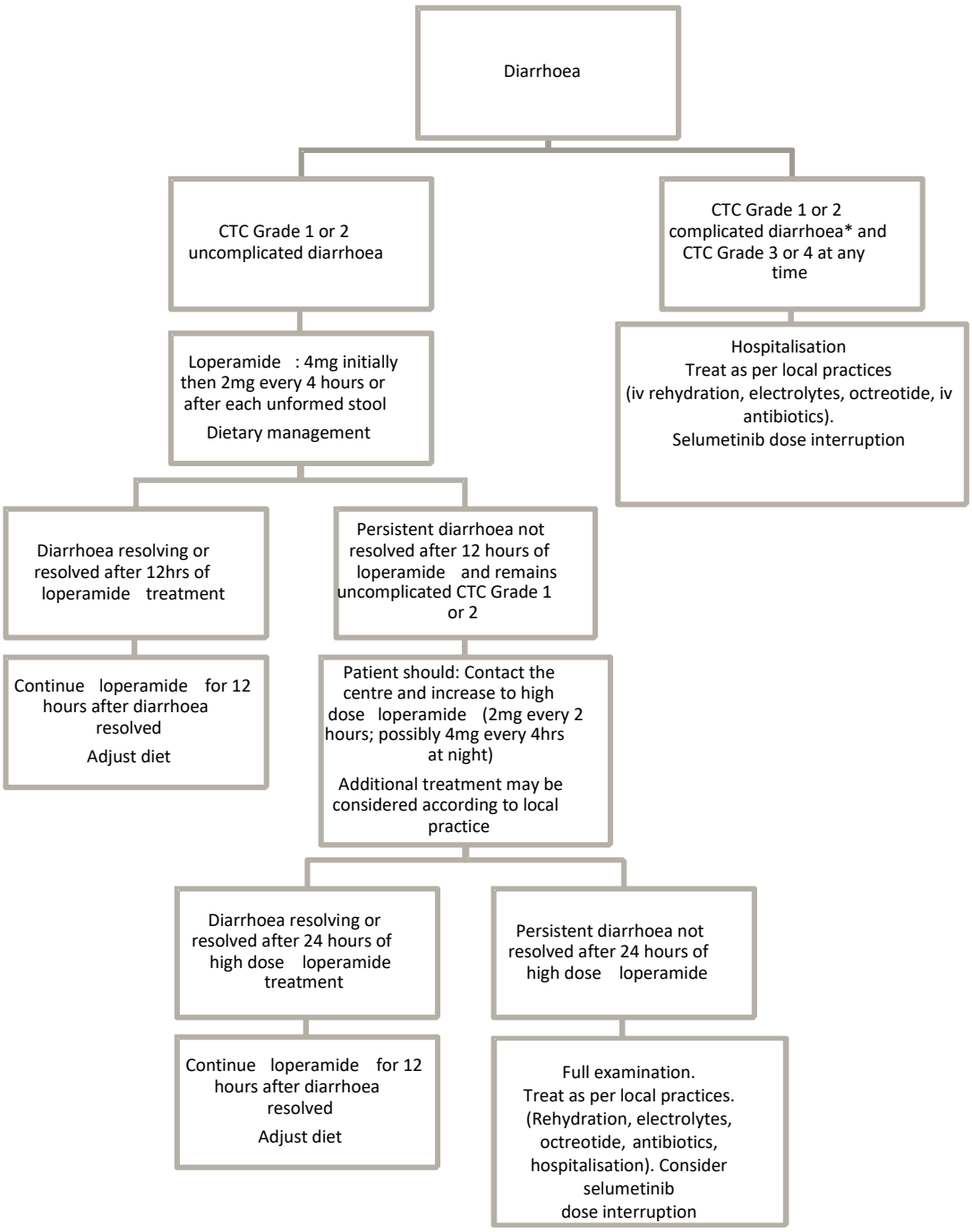
Appendix 3:

Guidance for the management of patients with rash



Appendix 4:

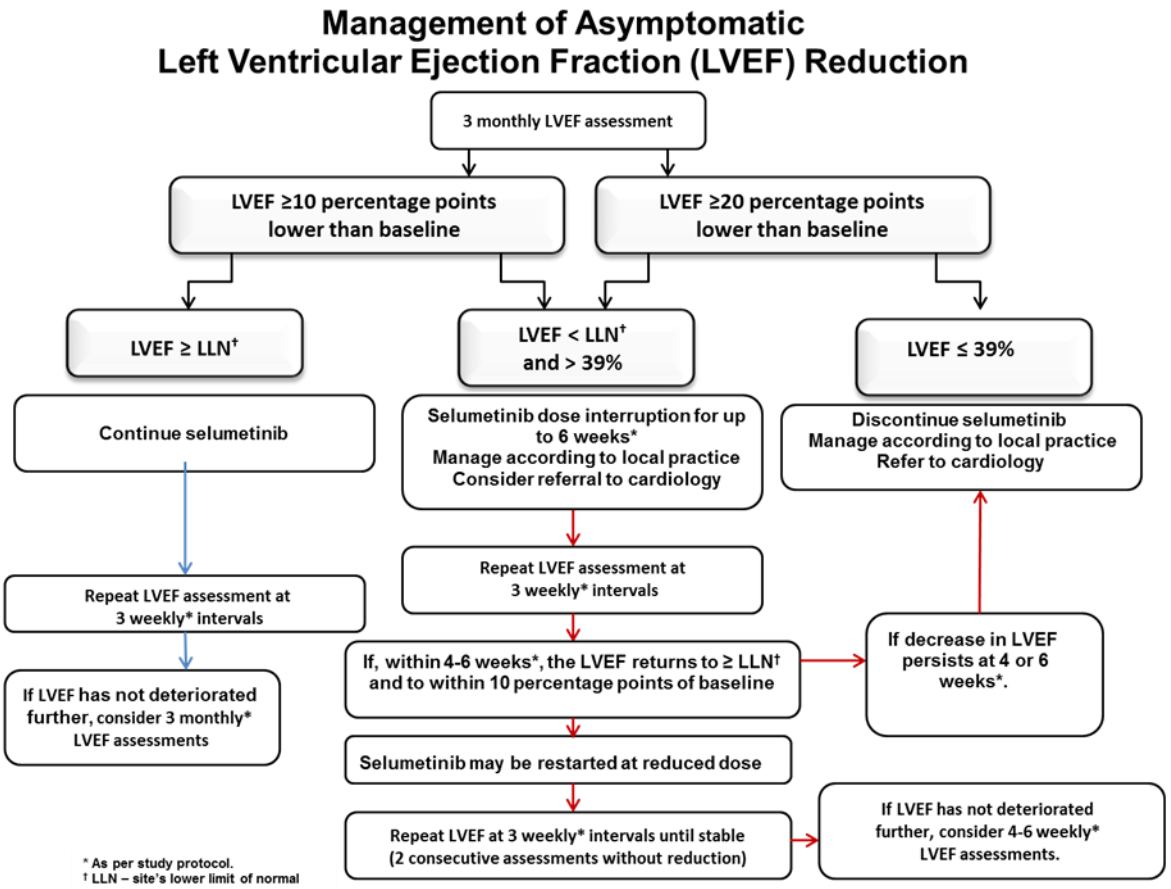
Guidance for the management of patients with diarrhoea



*Diarrhoea becomes complicated by associated vomiting or inability to take oral fluids; marked abdominal distension or cramping; bloody stools, fever or symptoms of hypotension

Appendix 5:

Guidance for management of patients with an asymptomatic reduction in LVEF



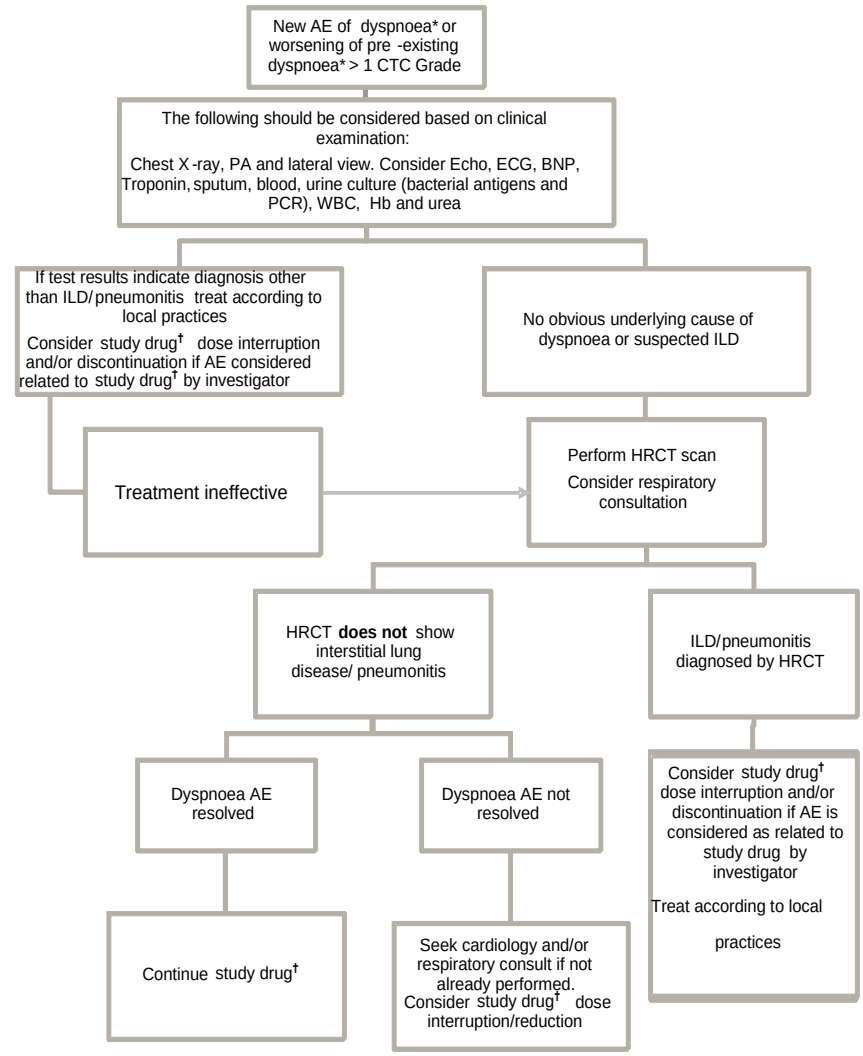
Appendix 6:

Guidance for management of patients with dyspnoea

Guidance for management of patients with dyspnoea*

*** Not considered related to disease under study**

† Includes selumetinib/placebo or combination treatment, as appropriate

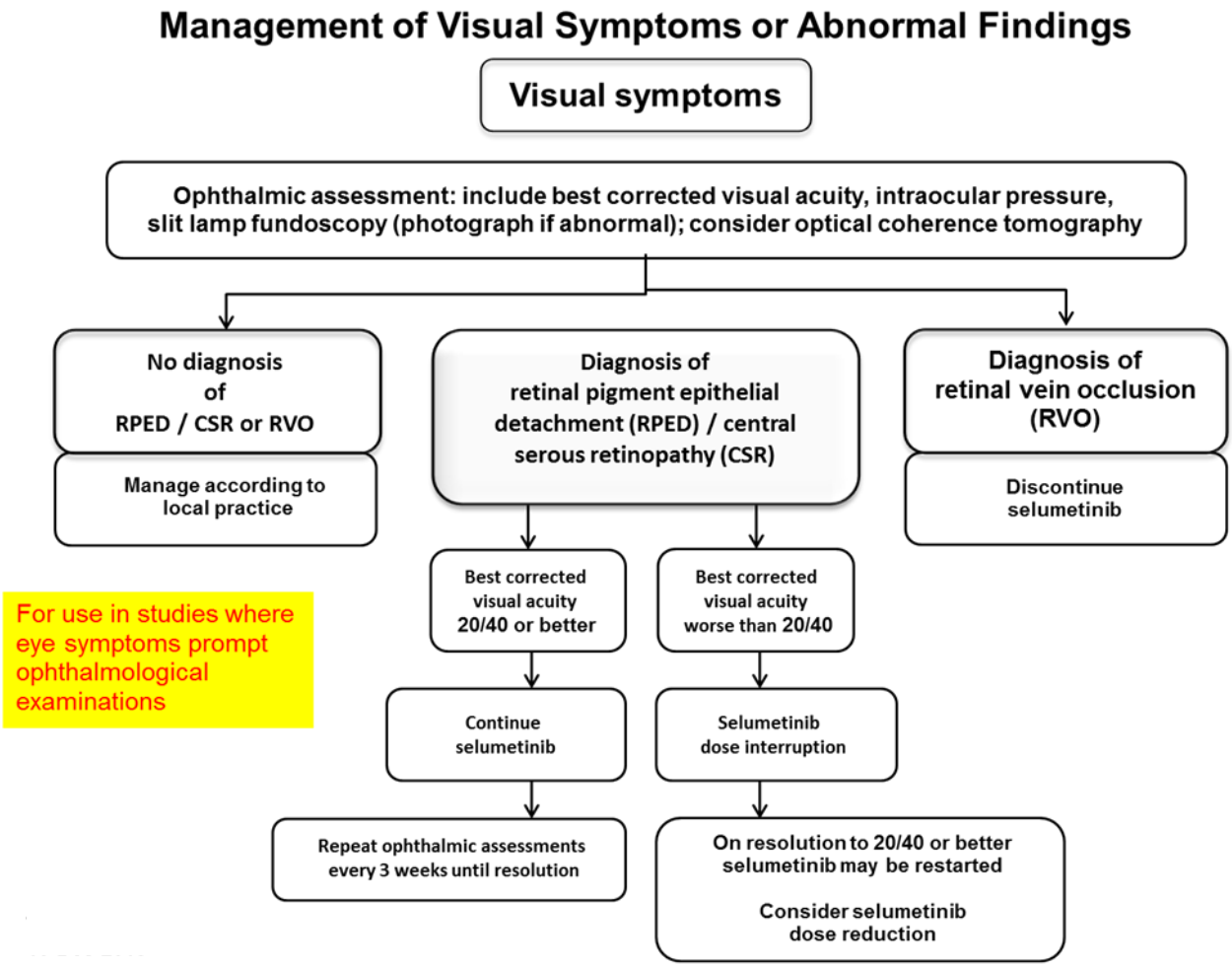


BNP: Brain Natriuretic
CTC: National Cancer Institute common toxicology
Echo: Echocardiography
Hb: Haemoglobin
HRCT: High resolution computerised

ILD: Interstitial Lung
PA: posteroanterior
PCR: Polymerase chain
WBC: White blood cells

Appendix 7:

Guidance for management of patients with visual symptoms



Appendix 8:

Oral Care Recommendations for Patients treated with Selumetinib

Patients should be encouraged to take responsibility for their own oral care wherever possible. This may require frequent encouragement and education. The general recommendations of Rubenstein et al (2004) are to maintain a clean and pain-free mouth which reduces patient discomfort and helps prevent infection and promote dietary intake. Evidence from the literature regarding implementation and efficacy of oral protocols and patient education, suggest that patients who are taught oral care protocols perform oral care more diligently, take more responsibility for their care and may show an improvement in oral symptoms.

Prevention, early diagnosis and management of stomatitis may reduce the need for dose interruption and / or reductions of the study medications due to severe stomatitis and so allow the patient to continue on the study drugs. It is strongly recommended that patients receive advice regarding daily oral health care regimes, both before and during treatment.

Mouthwashes:

Patients with a healthy mouth may use non-alcoholic mouthwash several times (4 to 6 times daily, or according to the instructions) daily, e.g. after each meal, during the study.
Saline mouthwashes (Sodium chloride 0.9%) should be preferred in cases of stomatitis, and should be used at a different time to toothbrushing, e.g. after tea.

Use of a mouthwash immediately after selumetinib intake is recommended.
The tongue can be gently brushed (if not sore) with a soft toothbrush.
Patients with, or at risk of stomatitis should not use commercial / over-the-counter mouthwashes because of the alcohol content and astringency. Chlorhexidine mouthwashes are not recommended for the treatment of established stomatitis.
The mouth should be regularly inspected by the patient and healthcare professionals.

Smoking should be strongly discouraged; patients should be offered help with smoking cessation if necessary in the form of nicotine replacement therapy or referral to smoking cessation services.

A high alcohol intake should be discouraged and patients advised to avoid painful stimuli such as spicy foods, hot food and drink.

Dental care:

Dentate patients:

- Patients who are free from dental problems may be at less risk of stomatitis.
- Teeth should be brushed twice daily with a fluoride toothpaste and soft toothbrush, in the morning before breakfast and last thing in the evening before bed, about 30 minutes after eating. Toothbrush should be replaced regularly at least every 3 months but patients with stomatitis should change their toothbrush every 4 - 6 weeks.
- Use of soft toothbrush is recommended
- Dental floss should be used once daily (caution in patients with coagulopathies including a low platelet count)

Edentulous patients:

- Dentures should be left out whilst at rest.
- Dentures should be cleaned thoroughly twice daily (before and after soaking overnight) and after every meal using a soft toothbrush and denture cleaner water
- Dentures should be soaked overnight in a mild denture-soaking solution.

In the event of sore mouth or stomatitis:

- Consider treating stomatitis at an early stage (CTCAE grade 1) or as soon as the patient complains of a sore mouth.
- Consider using oral topical analgesic anaesthesia with or without topical steroids, antiviral and/or antifungal medications depending on the patient's clinical condition and the local standard medical practice.

Appendix 9:

Medications to Avoid with Selumetinib

Inhibitors of CYP1A2, CYP2C19 or CYP3A4

Changes to, or addition of, the following medications should be avoided, unless clinically indicated:

Table 1 Inhibitors of CYP1A2, CYP2C19 or CYP3A4

CYP1A2	CYP2C19	CYP3A4
Fluvoxamine		Indinavir
Ciprofloxacin		Nelfinavir
		Ritonavir
		Clarithromycin
		Itraconazole
		Ketoconazole
		Nefazodone
		Saquinavir
		Suboxone
		Telithromycin
		Aprepitant
		Erythromycin
		Fluconazole
		Grapefruit juice
		Verapamil
		Diltiazem

Inducers of CYP1A2, CYP2C19 or CYP3A4

Changes to, or addition of, the following medications should be avoided, unless clinically indicated:

Table 2 Inducers of CYP1A2, CYP2C19 or CYP3A4

CYP1A2	CYP2C19	CYP3A4
Methylcholanthrene	Carbamazepine	Efavirenz
Modafinil	Norethindrone	Nevirapine
Nafcillin	Prednisone	Barbiturates
Beta-naphthoflavone	Rifampin	Carbamazepine
Omeprazole		Glucocorticoids
		Modafinil
		Oxcarbazepine
		Phenobarbital
		Phenytoin
		Pioglitazone
		Rifabutin
		Rifampin
		St John's wort
		Troglitazone

AA

Thu 18/06/2020 20:44
Astor, Alex
Re: SelPac amendment 10. - protocol v7

To Handley, Louise
Cc Sponsor

Dear Louise,

Yes apologies, please accept this email as confirmation as Sponsor Representative for the attached protocol.

Alex
Alex Astor
Research Support Office

From: Handley, Louise
Sent: Thursday, June 18, 2020 8:21:57 PM
To: Astor, Alex
Cc: Sponsor
Subject: RE: SelPac amendment 10. - protocol v7
Hi Alex,
Just to keep our document controller and QA happy, could you also confirm approval of the attached protocol, that was submitted as part of the amendment.
Protocol v7, dated 13th May 2020 as per the protocol approval page (page 2)?
BW
Louise
From: Astor, Alex
Sent: 18 June 2020 20:18
To: Sponsor ; 'Louise.Handley@liverpool.ac.uk'
Subject: RE: SelPac amendment 10. - AZ permission to proceed
Dear Lara and Louise,
Apologies for the delay in responding. Please accept this email as confirmation from Sponsor Representative for this amendment.
Regards,
Alex
From: Sponsor <sponsor@liverpool.ac.uk>
Sent: 17 June 2020 08:09
To: Astor, Alex <astor@liverpool.ac.uk>
Subject: FW: SelPac amendment 10. - AZ permission to proceed
Hi Alex,
Louise sent a request to approve the Selpac protocol could you approve please its been seen by Tony.
Many thanks
Lara Lavelle-Langham
Clinical Research Governance Manager
Research Support Office
University of Liverpool / Liverpool Joint Research Office
2nd Floor Block C Waterhouse Building
3 Brownlow Street
Liverpool L69 3GL
Tel: 0151 794 8373

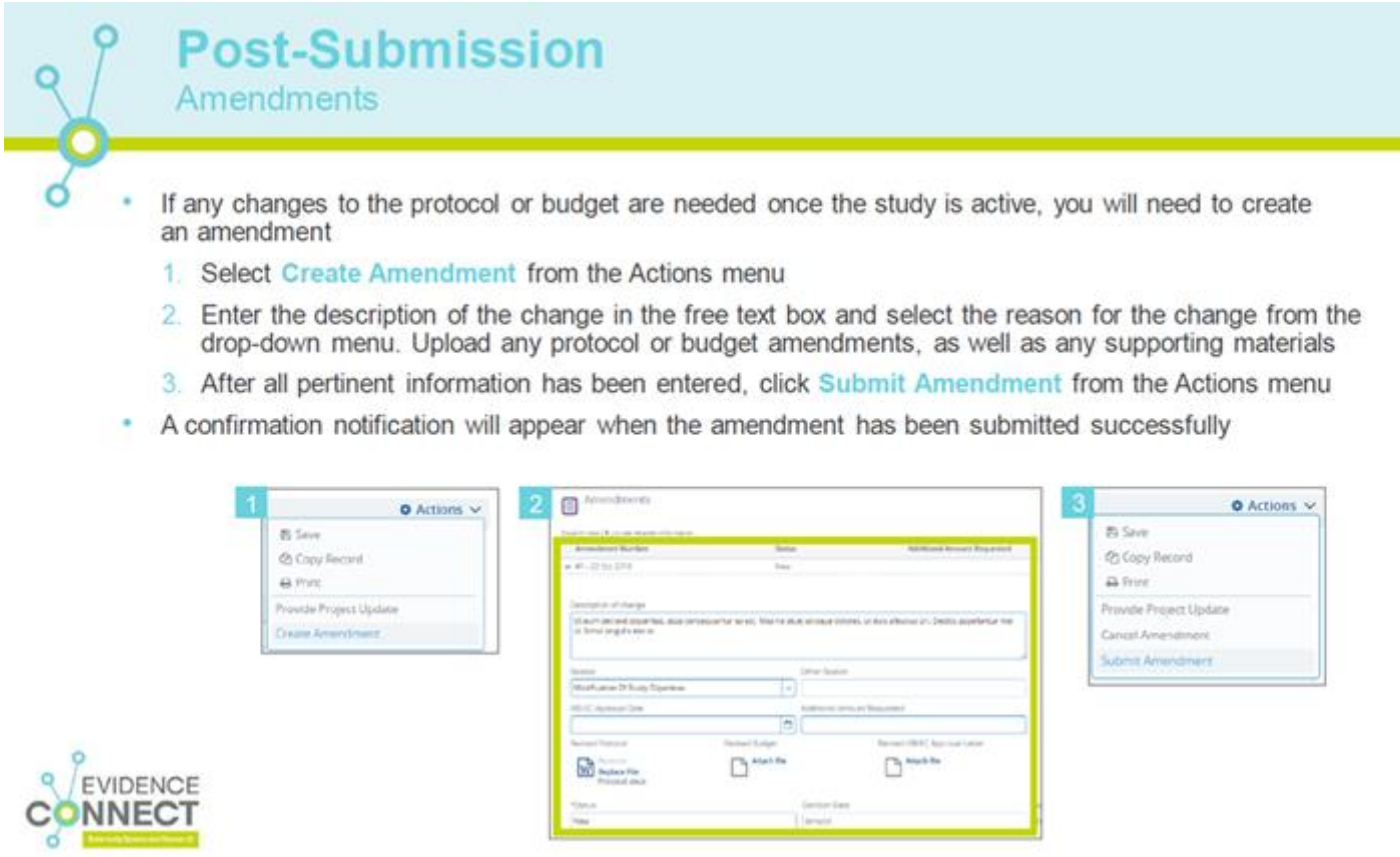
Email: Lara.Lavelle-Langham@liverpool.ac.uk
sponsor@liverpool.ac.uk
Web: Research Support Office / Liverpool Health Partners
UoL Sponsor COVID-19 updates – Please visit the Research Sponsorship website here for latest guidance on Sponsored research during the Coronavirus Pandemic
COVID-19 Updates – please visit the RSO website here for information on COVID-19 **research support**, including major COVID-19 funding Calls.

Making an Impact 2020 enables staff to engage in a programme of activities tailored to their research impact needs, interests and ambitions.
There are 57 different sessions to choose from! **Register now** so that you don't miss out:
https://bit.ly/MAI2020prog
From: Handley, Louise
Sent: 17 June 2020 07:37
To: Sponsor <sponsor@liverpool.ac.uk>
Subject: FW: SelPac amendment 10. - AZ permission to proceed
Hi Lara,
Please find AZ approval for the SelPac amendment 10.
If you see Alex would you ask could he approve the protocol page – I have sent an email but he is probably not sure what this approval request is for.
Thanks
Louise
From: Ranjan, Bhavana <bhavana.ranjan@astrazeneca.com>
Sent: 16 June 2020 12:31
To: Handley, Louise <Louise.Handley@liverpool.ac.uk>
Subject: RE: SelPac amendment 10. - AZ permission to proceed
Dear Louise,
Not sure if you had a chance to log into Evidence Connect. I confirm that the protocol amendment submited has been approved.
Please can you let me know when you have submitted the protocol approval. We still need to review the Milestone date in Evidence Connect.
Kind regards,
Bhavana
Bhavana Ranjan
ESR Coordinator – Oncology

AstraZeneca
Medical Affairs | UK Oncology Business
Horizon Place, 600 Capability Green, Luton, LU1 3LU
M: +44 7384907711
From: Handley, Louise <Louise.Handley@liverpool.ac.uk>
Sent: 04 June 2020 14:30
To: Ranjan, Bhavana <bhavana.ranjan@astrazeneca.com>
Subject: RE: SelPac amendment 10. - AZ permission to proceed
Brilliant ☺

From: Ranjan, Bhavana <bhavana.ranjan@astrazeneca.com>
Sent: 04 June 2020 14:30
To: Handley, Louise <Louise.Handley@liverpool.ac.uk>
Subject: RE: SelPac amendment 10. - AZ permission to proceed
Thanks Louise
I have started the amendment review and have requested a quick turnaround. I will be in touch once I have received the feedback.
Kind regards,
Bhavana
Bhavana Ranjan
ESR Coordinator – Oncology

AstraZeneca
Medical Affairs | UK Oncology Business
Horizon Place, 600 Capability Green, Luton, LU1 3LU
M: +44 7384907711
From: Handley, Louise <Louise.Handley@liverpool.ac.uk>
Sent: 04 June 2020 13:56
To: Ranjan, Bhavana <bhavana.ranjan@astrazeneca.com>
Subject: RE: SelPac amendment 10. - AZ permission to proceed
Hi Bhavana,
Think I have don't it! I know everyone is busy at AZ but if they could let us know the outcome of the review asap it would really help given tight timelines to get this in and approved before EOT declaration
Thanks, as always for all your help,
Louise
From: Ranjan, Bhavana <bhavana.ranjan@astrazeneca.com>
Sent: 04 June 2020 13:37
To: Handley, Louise <Louise.Handley@liverpool.ac.uk>
Subject: RE: SelPac amendment 10. - AZ permission to proceed
Dear Louise,
Thanks for sending the protocol amendment. Please can I request you upload this into evidence connect under amendment node.



Kind regards,
Bhavana
Bhavana Ranjan
ESR Coordinator – Oncology

AstraZeneca
Medical Affairs | UK Oncology Business
Horizon Place, 600 Capability Green, Luton, LU1 3LU
M: +44 7384907711

From: Handley, Louise <Louise.Handley@liverpool.ac.uk>
Sent: 04 June 2020 12:26
To: Ranjan, Bhavana <bhavana.ranjan@astrazeneca.com>
Subject: SelPac amendment 10. - AZ permission to proceed

Dear Bhavana,
The CI and sponsor would now like to close SelPac.
We propose to amend LPLV definition to: '*The end of the trial is defined to be the date on which all patients have been followed up until death* ***or until 14 months from the time the last patient has completed trial treatment, if this occurs first'***
This will allow us to declare end of trial on the **04/08/2020.**
We currently have 7 pts. still in FU.

After completing the preliminary analysis and review of overall survival curves the TMG felt that no additional value will be added with the longer follow up period.
The statisticians also confirmed that the number of remaining patients alive is not big enough to change the interpretation of the analysis results.
In addition to the above the following changes have also been made to the protocol:
a. Contact details updated.
b. Paragraph added to provide information on trials unit merger.
c. Update to translational sample storage location.
d. Update to the wording for LPLV and trial closure.
e. Update to statistical section 10.4 for consistency with LPLV statement.
Please can you confirm AZ are happy for us to proceed with this amendment?
Best wishes,
Louise

Louise Handley
TACE-3 & SelPac Trial Coordinator | **Liverpool Clinical Trials Centre** | **The University of Liverpool**
Liverpool Clinical Trials Centre, University of Liverpool, Block C Waterhouse Building, 1-3 Brownlow Street, Liverpool, L69 3GL
T: 0151 794 8935 | **E:** Louise.Handley@liverpool.ac.uk

AstraZeneca UK Limited is a company incorporated in England and Wales with registered number:03674842 and its registered office at 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge, CB2 0AA.
This e-mail and its attachments are intended for the above named recipient only and may contain confidential and privileged information. If they have come to you in error, you must not copy or show them to anyone; instead, please reply to this e-mail, highlighting the error to the sender and then immediately delete the message. For information about how AstraZeneca UK Limited and its affiliates may process information, personal data and monitor communications, please see our privacy notice at www.astrazeneca.com

---

AstraZeneca UK Limited is a company incorporated in England and Wales with registered number:03674842 and its registered office at 1 Francis Crick Avenue, Cambridge Biomedical Campus, Cambridge, CB2 0AA.
This e-mail and its attachments are intended for the above named recipient only and may contain confidential and privileged information. If they have come to you in error, you must not copy or show them to anyone; instead, please reply to this e-mail, highlighting the error to the sender and then immediately delete the message. For information about how AstraZeneca UK Limited and its affiliates may process information, personal data and monitor communications, please see our privacy notice at www.astrazeneca.com

NA

Tue 16/06/2020 09:18
Needham, Alexander [aneedham]
RE: SelPac Amendment 10 - Trial Statistician Protocol v7 Sign Off Request

HI Louise,

I confirm my approval.

BW

Mr Alexander Needham
Trial Statistician

Liverpool Clinical Trials Centre
Cancer Research UK Liverpool Cancer Trials Unit
University of Liverpool
1st floor Block C, Waterhouse Building
3 Brownlow Street
Liverpool
L69 3GL

Please note I work Monday to Wednesday

Tel: +44(0)151 7957505
Email: A.Needham2@liverpool.ac.uk
Website: www.lctu.org.uk

From: Handley, Louise <lhandley@liverpool.ac.uk>
Sent: 09 June 2020 20:31
To: Needham, Alexander [aneedham] <A.Needham2@liverpool.ac.uk>
Cc: SelPac <selpac@liverpool.ac.uk>
Subject: SelPac Amendment 10 - Trial Statistician Protocol v7 Sign Off Request

Dear Alex

Please could I ask for email confirmation of Trial Statistician Study Protocol Sign Off for the attached protocol v7, dated 13th May 2020 as per the protocol approval page (page 2)?

Due to the covid situation an SOP deviation has been raised and approved to forgo the requirement for wet ink signatures.

With kind regards
Louise

Louise Handley

TACE-3 & SelPac Trial Coordinator | **Liverpool Clinical Trials Centre** | **The University of Liverpool**
Liverpool Clinical Trials Centre, University of Liverpool, Block C Waterhouse Building, 1-3 Brownlow Street, Liverpool, L69 3GL
T: 0151 794 8935 | **E:** Louise.Handley@liverpool.ac.uk

PN

Mon 29/06/2020 12:30

Paul Nathan <nathan.pd@gmail.com>

Re: UoL001077 169996 15/LO/0159 - SelPac Amendment 10 - Sponsor Approval

Hi Louise

Protocol changes look fine to me. Approved. With thanks. Paul

On Mon, 8 Jun 2020 at 13:22, Handley, Louise <Louise.Handley@liverpool.ac.uk> wrote:

Hi Dr Nathan

Sponsor has approved the amendment documentation for SelPac – LPLV update, which will allow for a LPLV date of the 04/08/2020.

I will send the updated IRAS REC form for you to sign ahead of submission – summary of changes as attached.

Best wishes

Louise

Louise Handley

TACE-3 & SelPac Trial Coordinator | Liverpool Clinical Trials Centre | The University of Liverpool
Liverpool Clinical Trials Centre, University of Liverpool, Block C Waterhouse Building, 1-3 Brownlow Street, Liverpool, L69 3GL

T: 0151 794 8935 | **E:** Louise.Handley@liverpool.ac.uk

From: Sponsor
Sent: 08 June 2020 12:07
To: Handley, Louise <lhandley@liverpool.ac.uk>; Astor, Alex <astor@liverpool.ac.uk>
Cc: SelPac <selpac@liverpool.ac.uk>; Rawcliffe, Charlotte <clr001@liverpool.ac.uk>
Subject: RE: UoL001077 169996 15/LO/0159 - SelPac Amendment 10 - Sponsor Assessment Form

Dear Louise,

RE: SelPac: A randomised three-arm, open label, Phase II study of continuous Selumetinib versus continuous or interrupted Selumetinib in combination with weekly Paclitaxel in Metastatic Uveal Melanoma- UoL001077

Amendment 10 has now been reviewed and approved by the University as Sponsor. Please find attached the attached updated amendment form. Alex, please could you respond to confirm approval.

The amendment has been approved with the following recommendations.

- Submission to REC is required
- Submission to MHRA and BFARM is required

If you could provide REC, BFARM and MHRA approval when available it would be greatly appreciated.

Many thanks

Lara Lavelle-Langham

Clinical Research Governance Manager

Research Support Office

University of Liverpool / Liverpool Joint Research Office

2nd Floor Block C Waterhouse Building

3 Brownlow Street

Liverpool L69 3GL

Tel: 0151 794 8373

Email: Lara.Lavelle-Langham@liverpool.ac.uk

sponsor@liverpool.ac.uk

Web: Research Support Office / Liverpool Health Partners

UoL Sponsor COVID-19 updates – Please visit the Research Sponsorship website here for latest guidance on Sponsored research during the Coronavirus Pandemic

COVID-19 Updates – please visit the RSO website here for information on COVID-19 **research support**, including major COVID-19 funding Calls.

Making an Impact 2020 enables staff to engage in a programme of activities tailored to their research impact needs, interests and ambitions.
There are 57 different sessions to choose from! **Register now** so that you don't miss out:
https://bit.ly/MAI2020prog

From: Handley, Louise
Sent: 05 June 2020 11:38
To: Sponsor <sponsor@liverpool.ac.uk>
Cc: SelPac <selpac@liverpool.ac.uk>; Rawcliffe, Charlotte <clr001@liverpool.ac.uk>
Subject: 169996 15/LO/0159 - SelPac Amendment 10 - Sponsor Assessment Form

Hi Lara,

RE: SelPac Amendment 10 (UK) corresponding to Amendment DE03 (Germany)

Please find attached the Sponsor Assessment Form with supporting documents for review.

SOP deviations for email review and approval of amendment and protocol development documentation instead of wet-ink signatures, in relation to COVID-19 have been approved and attached for your reference.

The amendment to the protocol, v7 dated 13th May 2020, is primarily to consider an update to the LPLV definition.

The IRAS REC and CTA forms have also been updated to reflect the protocol changes (draft attached with changes highlighted in yellow).

The last pt. ended treatment on the 04/06/2019 so we will be in a position to declare EOT on the 04/08/2020 subject to all amendment approvals in the UK and Germany

To note: the protocol has been sent to AZ we are currently waiting on their approval. They have stated they will make every effort to allow for a quick review turn around.

We will not submit the amendment until AZ approval has been received.

Please feel free to contact me if you have any questions or require any further information.

Best wishes,

Louise

Louise Handley

TACE-3 & SelPac Trial Coordinator| **Liverpool Clinical Trials Centre** | **The University of Liverpool**
Liverpool Clinical Trials Centre, University of Liverpool, Block C Waterhouse Building, 1-3 Brownlow Street, Liverpool, L69 3GL

T: 0151 794 8935 | **E:** Louise.Handley@liverpool.ac.uk

--
Dr. Paul Nathan MBBS, PhD, FRCP
Consultant Medical Oncologist
Mount Vernon Cancer Centre
Rickmansworth Road
Northwood,
Middlesex
HA6 2RN
UK

tel +44(0)20 3826 2444