VALISEEK LIMITED

PRODUCT: VAL401

CLINICAL STUDY PROTOCOL

A Phase II Study to Assess the Efficacy, Safety and Tolerability of VAL401 in the treatment of patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) after failure of at least one prior chemotherapeutic regimen.

Protocol No: VAL401-001

Version No: 2.0

Version Date: 22 November 2016

Sponsor Signatures

I have reviewed and approve the protocol

ValiSeek Limited

c/o Valirx plc

16 Upper Woburn Place

London, WC1H 0BS

UK

Principal Investigator Declaration

I have read this protocol and agree that it contains all the necessary details for carrying out this study. I will conduct the study as described and will complete the study within the time designated. I verify that I am suitably qualified by education, scientific and medical training and experience to conduct the study. Documentation of my qualifications and professional affiliations are contained in my up-to-date curriculum vitae.

I will provide the supplied copies of the protocol, including future protocol amendments, and all information relating to non-clinical, and clinical experience when available (e.g. in updated editions of the Investigator's Brochure), to all staff in my unit involved in the conduct of this study. I will discuss this material with them to ensure that they are fully conversant with medical treatment and study design, and that they will handle the data and information generated in the study confidentially.

I will conduct the study in accordance with GCP, the Declaration of Helsinki, and the moral, ethical and scientific principles that justify medical research. The study will be conducted in accordance with the relevant laws and regulations relating to clinical studies and the protection of patients. All patients will be informed comprehensively about the nature of the study and will give their written consent to participate before entry into the study. They will be informed that they may withdraw from the study at any time. I will use only the information sheet and consent form approved by ValiSeek and the Ethics Committee (EC) for this study. I will supply ValiSeek with any material written by myself (e.g. summary of study) which is given to the EC in support of the application.

Where applicable, the patient information contained in clinic records, reports and manuscripts will be transcribed to the case report forms (the case report form may be the original source document for specified items). Either I or an appointed person will attest to the authenticity of the data and accuracy and completeness of the transcription by signing the case report form. I agree to the audit and monitoring procedures that involve verification of such study records against original records. Should it be requested by government regulatory agencies, I will make available additional background data from my records, and where allowed, from the hospital or institution where the study was conducted.

I understand that the case report forms and other data pertinent to this study are the property of ValiSeek and are confidential. I will supply ValiSeek (or their delegates) with the study data in such a way that the patient cannot be personally identified.

Investigator Signature:

Other Contact Information

Full contact details for each Investigational site, the Sponsor, Medical Monitor and other key coordinating and operational personnel involved in this clinical trial (including vendors), will be maintained and available for reference in the Trial Master File and in each Site Study File.

Protocol Synopsis

Protocol No:
VAL401-001

Study Title:
A Phase II Study to Assess the Efficacy, Safety and Tolerability of VAL401 in the treatment of patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) after failure of at least one prior chemotherapeutic regimen.

Investigational Product:
VAL401. VAL401 is a formulation of Risperidone in a lipid filled capsule for oral administration.

Phase of Development:
II

No of Sites:
2

No of Patients:
20

Study Objectives and Endpoints:
The objectives of this study are to assess the safety, tolerability, pharmacokinetics (PK) and efficacy of VAL401 in patients with locally advanced or metastatic non-small cell lung cancer.

Objective	Endpoint
Primary: • Progression-free survival (PFS)	• As assessed by RECIST 1.1 criteria. PFS will be defined as the time from randomisation to disease progression (or death if the patient died before progression)
Secondary: • To evaluate the pharmacokinetics of VAL401 • To assess potential disease modifying activity • To determine the safety and tolerability of VAL401 • To evaluate patient quality of life during VAL401 treatment • Overall Survival	• Assessment of pharmacokinetic variables in collected blood samples (including C_{max}, C_{min}, AUC) on Day 1 and Day 15 of Cycle 1. • Objective tumour response rates according to RECIST 1.1 including time to objective response and duration of objective response; or disease control (defined as a patient with objective response or stable disease) according to RECIST version 1.1 including duration of disease control • Ongoing evaluation of AEs during treatment and follow up • Changes in patient quality of life measured by HRQoL assessment EORTC QLQ – C30 provided in Georgian under license from EORTC
Exploratory: • Biomarker testing	• Testing of germline DNA in single blood sample at Day 0 for biomarker assessment. Testing of historic tumour biopsy material where available.

Study Design:

This is a Phase II, open label study to assess the efficacy, safety and tolerability of VAL401 in the treatment of patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) after failure of at least one prior chemotherapeutic regimen. Eligible patients will be enrolled as a single cohort and treated with VAL401, given as oral capsules.

Each patient will be dosed according to the schedule of: Day 1: 2 mg in a single daily dose; Day 2: 4 mg in a single daily dose; Day 3: 6 mg in a single daily dose; Day 4: 8 mg in a single daily dose; Day 5 and onwards: 10 mg in a single daily dose.

If a patient experiences a DLT, the dose will be reduced to the previous acceptable dose, and the patient will remain on this personal MTD for the remainder of the study.

VAL401 is supplied as 5 mg and 1 mg dose capsules, each day's individual dose composed of the relevant combination of 1 mg and 5 mg capsules to total the required level.

All patients will remain on 10 mg as a single daily dose (or their personal MTD if reached) until they experience disease progression or unacceptable toxicity.

Dose Limiting Toxicity

The maximum feasible dose which may be administered is 10 mg per day. Should this dose be reached without the need to de-escalate the dose due to DLT, it will be termed the Maximum Administered Dose (MAD).

Safety Evaluations will be conducted daily during the dose escalation period (a minimum of Day 1 – Day 5 of Cycle 1), weekly for the remainder of cycle 1, and fortnightly thereafter. All events and suspected DLTs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

A DLT is defined as a VAL401-related Grade 3 or 4 adverse event that, in the opinion of the Investigator represents a clinically significant hazard to the subject, with the following **exceptions** as considered appropriate:

- Grade 3 or 4 laboratory abnormalities, which resolve spontaneously or can be corrected with appropriate treatment (such as electrolytes). For example, an event returns to baseline or to Grade 1 at the next assessment.
- Symptomatic adverse events, such as nausea, vomiting and diarrhea, if they can be reduced to less than Grade 3 with standard supportive measures, such as anti-emetics and anti-diarrhoeals within 72 hours.

Qualifying toxicity events must be considered to be clinically relevant e.g. in duration, and likely to be related to treatment with VAL401. DLT events will also be considered in terms of what is considered to be an appropriate next escalation step: in the case where the Investigator considers a daily escalation of 1 mg instead of 2 mg per day in the dose escalation period of Cycle 1, the toxicity of concern should be declared a DLT.

Dose Escalation

During Cycle 1 of treatment the following escalation steps are recommended in the absence of VAL401-related events which would lead to a more cautious dose escalation:

Cycle 1; Day	Daily Dose	Capsules administered
1	2 mg	2 x 1 mg
2	4 mg	4 x 1 mg
3	6 mg	1 x 5 mg + 1 x 1 mg
4	8 mg	1 x 5 mg + 3 x 1 mg
5 and subsequent	10 mg	2 x 5 mg

In the case where a potentially significant toxicity which is not a DLT, or a trend in toxicities seen, considered to be related to treatment with VAL401 occur and are considered to be a precursor of a clinically significant toxicity event; subsequent dose escalation steps *in that patient* may be more conservative (1mg per day increase until MTD reached, or a 24 hour delay until the next dose increase – at the discretion of the Investigator). This restriction may be reversed where there is no suggestion of a potentially clinical significant toxicity in the subsequent dose level.

Where a patient establishes a DLT, the dose should be reduced by one step, and the patient continued on this dose for the remainder of the study providing that the DLT has been resolved. This dose will be noted as the patient's personal MTD.

Duration of treatment

A maximum of 6 treatment cycles of 28 days is permissible within the design of this study. Patients whose disease has not progressed and who have not withdrawn from the treatment due to unacceptable toxicity will be able to continue to receive VAL401 at the discretion of the Investigator. Such patients will continue to be followed up for toxicity and continued response and may be transferred to an extended treatment protocol.

Study Assessments

The study will commence with a dosing schedule of VAL401 given orally as a capsule (or combination of capsules) according to the dose escalation described above on all days of a four week cycle.

Patients will visit the study sites on each day of the dose escalation period in Cycle 1, and fortnightly thereafter for the remainder of the 6 cycles of treatment for a clinical examination, recording of AEs and the Health related Quality of Life questionnaire (HRQoL). Laboratory screens will be assessed weekly during Cycle 1 and fortnightly thereafter. Tumour assessment including imaging where relevant will be assessed at Screening, after three cycles, and after 6 cycles. Follow up assessments will be conducted in accordance with RECIST 1.1 (Eisenhauer 2009).

A full PK profile will be taken after the first dose on Day 1 Cycle 1 and after dosing on Day 15 Cycle 1.

Patients will be asked to provide consent for access archived tumour tissue and blood samples where possible to allow for potential future biomarker and pharmacodynamics assessment.

Inclusion/Exclusion Criteria

The study will enroll patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) after failure of at least one prior chemotherapeutic regimen.

Inclusion Criteria:

- Diagnosis of Stage IIIB or Stage IV adenocarcinoma of the lung. Patients with mixed histology will be eligible if adenocarcinoma is the predominant histology.
- Prior chemotherapy for relapsed or metastatic NSCLC.
- Measurable disease according to RECIST version 1.1.
- Age≥18years.
- Life expectancy of at least 3 months.
- Negative human chorionic gonadotropin (hCG) test in women of childbearing potential (defined as women ≤ 50 years of age or history of amenorrhea for ≤ 12 months prior to study screening). Sexually active male and female patients of childbearing potential must agree to use an effective method of birth control e.g. barrier methods with spermicides, oral or parenteral contraceptives and/or intrauterine devices, during the entire duration of the study and for 1 month after the final administration of VAL401. Note that female patients may be surgically sterile (with appropriate documentation in the patient's medical records).
- Ability to give written, informed consent prior to any study-specific screening procedures with the understanding that the consent may be withdrawn by the patient at any time without prejudice.
- Patient is capable of understanding the protocol requirements, is willing and able to comply with the study protocol procedures, and has signed the informed consent document.

Exclusion Criteria:

- Radiotherapy or surgery (other than biopsy) within 4 weeks prior to Cycle 1 Day 1.
- Any chemotherapy regimens (including investigational agents) with delayed toxicity with 6 weeks of Cycle 1 Day 1, or received any chemotherapy regimens given continuously or on a weekly basis which have limited potential for delayed toxicity within 2 weeks prior to Cycle 1 Day 1. Palliative treatment regimens, and other concomitant drugs regimens are permitted with stable toxicity, and recording of all concomitant medications (including herbal).
- Pregnant or lactating female patients.
- Active hepatitis B or C or other active liver disease (other than malignancy).
- Any active, clinically significant, viral, bacterial, or systemic fungal infection within 2 weeks prior to Cycle 1 Day 1; other than CMV which may be present providing any required concomitant anti-viral treatment is recorded appropriately.
- Known human immunodeficiency virus positivity.
- History of clinically significant cardiac condition, including ischemic cardiac event, myocardial infarction or unstable cardiac disease with 3 months prior to Cycle 1 Day 1.
- Active brain metastases (defined as stable for <4 weeks and/or symptomatic and/or requiring treatment with anticonvulsants or steroids and/or leptomeningeal disease).
- Any known contraindications to Risperidone or patients who would not be eligible to receive the treatment as defined in the Special Warnings and Precautions section of the local label for Risperidone.
- Any medical history that in the Investigator's opinion would jeopardise compliance with the protocol.

Route of Administration, Dose Schedule and Duration

VAL401 is administered as an oral capsule, each capsule containing either 5 mg or 1 mg of active ingredient. The starting dose level of VAL401 is 2 mg as a single daily dose on Cycle 1 Day 1, with escalation of 2 mg per day to a maximum of 10 mg per day such that Cycle 1 Day 2 provides 4 mg VAL401 as a single daily dose, Day 3: 6 mg, Day 4: 8 mg, Day 5 and all subsequent days 10 mg as a single daily dose. The dose levels assessed in this study i.e. the dose and the dosing administration schedules, may be adjusted following the study dose escalation rules, based on review of on-going evaluation generated during the study.

The majority of VAL401 doses will be self-administered by the patient at home, with the investigator supplying sufficient capsules to the patient at each visit to maintain dosing until the next site visit.

Statistical Methods

Results will be presented using descriptive statistics. Data collected at screening and up to and including the Pharmacokinetic measurements collected on Day 15 Cycle 1 will be analysed during a preliminary analysis point when all patients have reached this stage. Final analysis will correlate all remaining data with the preliminary set after last patient, last visit and complete data lock.

All patients who receive at least one dose of VAL401 will be included in the safety analysis. Patients who fail to receive one full cycle of VAL401 therapy, for reasons other than DLT, may be replaced.

Schedule of Study Assessments

Assessment	Screening	Cycle 1								Subsequent Cycles (28 days each)				Final Study Visit[8]
		Day								Day				
	Day -28 to 0	1	2	3	4	5	6 to 14	15	16 to 28	1	2 to 14	15	16 to 28	
Informed consent	X													
Demographics	X													
Medical history	X													
Inclusion/exclusion	X													
ECOG PS	X							X		X		X		X
Physical examination[1]	X	X	X	X	X	X		X		X		X		X
Vital signs[2]	X	X	X	X	X	X		X		X		X		X
ECG (resting 12-lead)[3]	X	X	X	X	X	X		X		X		X		X
Clinical chemistry*	X					X		X		X		X		X
Haematology	X					X		X		X		X		X
Coagulation	X					X		X		X		X		X
Urinalysis*	X	X								X				X
Tumour assessment[4]	X	Perform after every 3 cycles +/- 1 week												X
Biomarker testing[5]	(X)													
Adverse events		X	X	X	X	X		X		X		X		X
Concomitant medication	X	X	X	X	X	X		X		X		X		X
VAL401 administration		X	X	X	X	X	X	X	X	X	X	X	X	
Pharmacokinetics[6]		X						X						
HRQoL[7]	X	X						X		X		X		X

Footnotes - General

- Assessments made on Day 1 of each cycle are to be conducted prior to VAL401 administration, unless specified otherwise.
- Additional assessments may be conducted as clinically indicated.
- (X) denotes optional.
- A tolerance of +/-1 day will be permitted for all study visits after completion of the dose escalation period and a tolerance of -1 day for all assessments relative to the study visit, unless specified otherwise.

* ***safety bloods will include HBV, HCV, HIV, CMV IgG IgM testing at Screening; female patients require a serum pregnancy test at Screening and urine pregnancy on Day 1 of each cycle***

Assessment Specific

1 Patient's height will be recorded at Screening. A full physical examination is required at Screening and prior to drug administration on Day 1 of each cycle; Symptom-directed physical examination is acceptable at other time-points. Weight will be recorded at Screening, on Day 1 of each cycle and at the Final Study Visit.

2 On Cycle 1, Day 1 vital signs (heart rate, BP, axillary temperature and respiration rate) will be assessed pre-dose and up to 1 hour after the VAL401 administration. On all other visit days during each cycle, vital signs will be assessed pre-dose only.

3 On Cycle 1, Day 1 a resting 12-lead ECG will be conducted pre-dose and up to 1 hour after the VAL401 administration. On all other visit days during each cycle, vital signs and 12-lead ECG will be assessed pre-dose only. Each assessment must be taken in triplicate at these time points.

4 CT or MRI performed at Screening and after every 3 cycles of treatment (+/- 1 week). Additional scans may be performed to confirm a Response or disease progression as appropriate for response assessment guidelines. Any requirement for confirmatory scans will typically be performed at the next protocolled assessment time point. Other informative markers may be taken as appropriate. Patients remaining on study after 6 cycles will have tumour assessment every 3-6 cycles.

5 Patients will be asked to give consent to perform future biomarker testing of archived and/or fresh tumour tissue where sample is available. Consenting patients will also have a 10 mL blood sample taken for preparation of a germ-line DNA sample at screening (recommended time-point only) for biomarker assessment.

6 PK sampling will be conducted at Cycle 1 at the following sample times. Two PK profiles may be taken (Day 1 and Day 15): each will not exceed up to 10 samples (taken up to 24 hours post drug administration; see example time points below). The actual time for each blood draw must be accurately recorded. Cycle 1, Day 15 measurement should be taken after between 7 and 14 days of continuous treatment.

- Cycle1, Day 1: pre-dose (0h) then 10, 15, 30 min, 1, 2, 4, 8, 10 and 24 h post-administration.
- Cycle 1, Day 15: pre-dose (0h) then 10, 15, 30 min, 1, 2, 4, 8, 10 and 24 h post-administration.

7 HRQoL survey EORTC QLQ – C30 version 3 will be required to be completed by the patient at the fortnightly site visits, at Screening and at the Final Visit.

8 The Final Study Visit should be performed 30 +/-3 days after the last dose of VAL401 to enable a final safety assessment.

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LIST OF ABBREVIATIONS

ADC	Adenocarcinoma
AE	Adverse Event
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under curve
BP	Blood Pressue
BRAF	Gene for which mutations are associated with lung cancer
BSA	Body Surface Area
CI	Confidence Interval
Cmax	Maximum serum concentration
Cmin	Minimum serum concentration
CNS	Central Nervous System
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DNA	De-oxy ribose nucleic acid
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
EGFR	Gene for which mutations are associated with lung cancer
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FFPE	Formalin fixed Parafin embedded
GCP	Good Clinical Practice
h	hour
HBV	Hepatitis B virus
hCG	human Chorionic Gonadotropin
HCV	Hepatitis C virus
HER2	Gene for which mutations are associated with lung cancer
HRQoL	Health Related Qulaity of Life
HSD10	Hydroxysteroid dehydrogenase type 10
ICH	International Conference of the Harmonisation of Technical Requirements for Medicinal Products for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Investigational Review Board
kg	kilogram
MAD	Maximum Administered Dose
mg	milligram
min	minute
mL	millilitre
mm	millimetre
MRI	Magnetic Resonance Imaging

MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NOAEL	No Adverse Effect Level
NSCLC	Non-small cell lung cancer
PFS	Progression-free Survival
PGMC	Propylene Glycol Monocaprylate
PK	Pharmacokinetics
pRBC	packed Red Blood Cells
PS	Performance Status
RECIST1.1	Response Evaluation Criteria in Solid Tumours
RET	Gene for which mutations are associated with lung cancer
RFA	Radiofrequency ablation
ROSI	Gene for which mutations are associated with lung cancer
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCC	Squamous cell carcinoma
sec	second
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SmPC	Summary of Product Characteristics
TKI	Tyrosine Kinase Inhibitors
WHO	World Health Organisation

1 INTRODUCTION

VAL401 is an equimolar mixture of Risperidone (active) and Rumenic Acid (excipient) in a liquid lipid filled capsule formulation that is under development by ValiSeek Limited, UK for the use as a therapy in the treatment of non-small cell lung cancer (adenocarcinoma).

1.1 Non-small cell lung cancer

Approximately one third of all cancer-related deaths are due to lung cancer, which accounts for more deaths each year than breast, prostate and colon cancer combined (Schiller et al., 2002). Whereas lung cancer in men peaked in the late 1980's, with a rate of over 50/100,000 men and falling by about a third thereafter to about 36/100,000 men, the rate in EU women has been growing over the past two decades. Causative factors of lung cancer are smoking, which is the main cause, responsible for more than 80% of cases, and there are also certain occupational factors such as exposure to asbestos, polycyclic aromatic hydrocarbons, crystalline silica and diesel exhaust. In fact, in 2012 diesel exhaust was classified as a type 1 carcinogen by the International Agency for Research against Cancer in Lyon, France (Sculier, 2013).

NSCLC is defined as a cancer of the lung which is not of the small cell carcinoma (oat cell carcinoma) type. The term "non-small cell lung cancer" applies to the various types of bronchogenic carcinomas (those arising from the lining of the bronchi). The World Health Organization (WHO) identifies multiple forms of NSCLC, but the major forms are squamous cell carcinomas (SCCs), adenocarcinoma (ADC) and large-cell (undifferentiated) carcinoma (Gazdar, 2010).

NSCLC accounts for 80-85% of all lung cancer cases (D'Addario, 2010). Approximately 90% of lung cancers among men and 80% among women are related to smoking. The majority of patients present with advanced disease. There is a considerable difference in the incidence across the different countries in Europe, with rates varying from 22 to 63% per 100,000 in men and from 5 to 33 per 100,000 per year in women, respectively.

The median survival of patients with untreated metastatic NSCLC is only about 4-5 months, with a survival rate at one year of about 10% (Schiller, 2002).

Symptoms of NSCLC

Lung cancer is often insidious, producing no symptoms until the disease is well advanced. In approximately 7-10% of cases, lung cancer is diagnosed in asymptomatic patients when a chest radiograph performed for other reasons reveals the disease. At initial diagnosis, 20% of patients have localized disease, 25% of patients have regional metastasis, and 55% of patients have distant spread of disease.

Signs and symptoms of lung cancers may be due to the primary tumour, locoregional spread, metastatic disease, or ectopic hormone production. Cough is reported to be the most common presenting symptom of lung cancer. Other respiratory symptoms include dyspnoea, chest pain, and haemoptysis. Haemoptysis has been described as the one symptom often prompting more rapid presentation (Corner, 2005).

Diagnosis of NSCLC

According to the ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, pathological diagnosis should generally be made according to the World Health Organisation (WHO) classification (Reck, 2014). Genetic alterations have been identified in many small subsets of NSCLC, such as ROSI, HER2, BRAF and RET alterations. Activating (sensitising) epidermal growth factor (EGFR) mutations are predictive for response to the EGFR tyrosine kinase inhibitors (TKIs) gefitinib, erltinib, and afatinib.

Standard tests for diagnosis include (after a complete history including smoking history and comorbidities, weight loss, performance status (PS) and physical examination) routine haematology, renal and hepatic function and bone biochemistry. Contrast-enhanced computed tomography (CT) scan of the chest and upper abdomen should be carried out. Dependent on the outcome, other imaging is conducted to determine potential CNS involvement and metastatic disease.

Treatment of NSCLC

Treatment depends upon the stage of the disease.

Stage I

Non-small cell lung cancer can often be removed with surgery. If there are other medical problems, or if the patient is not fit enough to have surgery, then radiotherapy may be given instead.

Chemotherapy is sometimes used after surgery (adjuvant chemotherapy) or before surgery and/or radiotherapy (neo-adjuvant).

Occasionally, radiofrequency ablation (RFA) may be used if other treatments are not suitable.

Stage II

It may be possible to remove stage 2 non-small cell lung cancer with surgery. Radiotherapy may be used for people who are not fit enough for surgery or choose not to have it. Chemotherapy is often given following surgery or radiotherapy.

Stage III

Non-small cell lung cancer can sometimes be removed with surgery, although this often is not possible if the cancer has metastasized. Neo-adjuvant or adjuvant chemotherapy may be given.

Stage IV

Chemotherapy should be offered to patients with stage IV NSCLC and good performance status to improve survival, disease control and quality of life. Chemotherapy for advanced NSCLC should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience. Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug. Docetaxel monotherapy should be considered if second-line treatment is appropriate for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy.

A significant advance in therapy has been made with the introduction of tyrosine kinase inhibitors (TKIs) for the treatment of NSCLC with activating mutation of the EGFR gene (targeted therapy). Chemotherapy and TKIs have no cross-resistance and hence administration of TKI has the same effect on overall survival whether administered as first-line or salvage treatment (Sculier, 2013).

1.2 Rationale for Treatment with VAL401 in non-small cell lung cancer

HSD10 is an enzyme which plays a protective role in stressed cells – with particular up-regulation under nutrient-limiting conditions such as those found in cancer (Carlson, 2015). This up-regulation in many cancers, in particular those with a hormone-driven growth factor such as adenocarcinomas, has long been described, and although HSD10 has been proposed as a druggable target (Carlson 2015, Kissinger, 2004), it is thus far unexploited, and no current cancer treatments have been designed to target HSD10.

HSD10 is predominantly mitochondrial in location in healthy cells, but under stressed conditions, migration to the mitochondrial membrane is observed, allowing access from the cytoplasm of the cell. This allows for a targeting mechanism in which the enzyme is accessible by many drugs only in cancerous (or similarly stressed) cells, and does not negatively affect healthy cell growth (Carlson, 2015).

During an enzyme assay screening process of a number of related drugs, Risperidone was selected as having substantial inhibitory activity on HSD10 both in oxidative and reductive functions of the enzyme.

In *in vitro* assays, Risperidone alone was found to have insufficient activity against the growth of cancer cells, but in formulation with the lipid excipient Rumenic Acid, biologically relevant activity against several adenocarcinoma cell lines (including those representing non-small cell lung cancer, small cell lung cancer, breast cancer, pancreatic cancer and prostate cancer) was observed and seen to be specific to adenocarcinoma cell lines. Rumenic Acid alone has no effect on the growth of cancer cell lines in our *in vitro* assays.

VAL401 is a formulation of Risperidone in a lipid filled capsule, with the lipid excipient containing the required Rumenic Acid component.

Subsequent *in vivo* assays confirmed the activity in non-small cell lung cancer with oral administration of VAL401 demonstrating a reduction in tumour growth rates in mice.

Both *in vitro* and *in vivo* studies have found that this unique formulation enables the anti-cancer activity of Risperidone to be accessed in a simple oral formulation. ValiSeek have chosen to advance VAL401 in Non-small Cell Lung cancer as a primary indication, where there is a high unmet medical need.

1.3 Summary of non-clinical development

VAL401 has been evaluated in both single and repeat dose toxicity studies in rats in which VAL401 was administered orally daily for up to one month at doses of 10 mg/kg/day – this is greater than an order of magnitude above the maximum dosage intended in this study (10 mg/day). These studies concluded the minimum NOAEL to be the maximum level tested (10 mg/kg/day), and demonstrated no effects beyond those predicted with the use of Risperidone.

Pharmacokinetic analysis in rats both in acute and chronic treatment demonstrated exposure to Risperidone in VAL401 to be comparable to that exposure reported for conventional Risperidone

formulations, concluding that the effects and toxicity are abridged and current guidelines for safety and tolerability will be used as an indicative starting point for this study.

Full details of the non-clinical pharmacology and toxicology programs for VAL401 can be found in the latest edition of the Investigator's Brochure.

1.4 Clinical Evaluation of VAL401

VAL401 has not been administered to humans before, although the API Risperidone has been administered in alternative formulations. This study is proposed using the safety and tolerability of the clinical API, Risperidone as a guideline, and the safety guidelines detailed in the SmPC for Risperidone should be considered integral to this protocol.

1.5 Rationale for Dose Selection

A NOAEL for VAL401 has been defined as a minimum of 10 mg/kg.

Allometric scaling employed to relate rat dose to human equivalent dose:

Conversion	Conversion factor	Rat dose	Human equivalent	70 kg Human patient	Margin over proposed maximum dose
b= 0.67*	0.156	10 mg/kg	1.56 mg/kg	109 mg/day	10
b=0.75	0.245	10 mg/kg	2.45 mg/kg	171 mg/day	17

*Use of the conversion factor 0.67 is the preferred approach for first in human studies by the FDA

Conversion of the dose ranges tested in the xenograft efficacy studies translates to an approximate maximum 10 mg per day (based on a calculation from a mouse 2mg/kg/day using a BSA calculation).

Risperidone is currently licensed for use as an anti-psychotic at up to 16 mg maximum dose per day, although prescription is more commonly between 4 and 8 mg dose per day, due to a clinically proven lack of greater anti-psychotic activity above 8 mg per day in the majority of patients.

By ensuring that our intended dosing regimen is within the current licensed use, VAL401 safety and tolerability can be confidently predicted.

Risperidone in conventional formulation is typically subjected to an initial dose escalation schedule with a ramping of daily dose from 2 mg to the required dose for efficacy at 24 hour intervals.

VAL401 is proposed to follow a comparable dose initiation schedule, with the starting dose of 2 mg/day, recommended to be taken in the evening to minimise quality of life effects of the temporary sedative effect of Risperidone, with a daily escalation in 2 mg increments to a maximum of 10 mg per day, or MTD if this is found to be lower for an individual patient.

The dose escalation and maintenance procedure in conjunction with close clinical monitoring and medical supervision is considered appropriate for the IMP under consideration.

1.6 Safety Guidance for Investigators

Investigators should refer to the latest edition of the IB for a full review of the potential risks associated with VAL401 and details of expected adverse events. The SmPC for Risperidone should be considered alongside the IB and this protocol, as adverse events associated with Risperidone usage can be expected to also occur with VAL401 usage.

2 STUDY OBJECTIVES

The objectives of this study are to assess the safety, tolerability, pharmacokinetics (PK) and efficacy of VAL401 in patients with locally advanced or metastatic non-small cell lung cancer.

Objective	Endpoint
Primary: • Progression-free survival (PFS)	• As assessed by RECIST 1.1 criteria. PFS will be defined as the time from randomisation to disease progression (or death if the patient died before progression)
Secondary: • To evaluate the pharmacokinetics of VAL401 • To assess potential disease modifying activity • To determine the safety and tolerability of VAL401 • To evaluate patient quality of life during VAL401 treatment • Overall Survival	• Assessment of pharmacokinetic variables in collected blood samples (including C_{max}, C_{min}, AUC) on Day 1 and Day 15 of Cycle 1. • Objective tumour response rates according to RECIST 1.1 including time to objective response and duration of objective response; or disease control (defined as a patient with objective response or stable disease) according to RECIST version 1.1 including duration of disease control • Ongoing evaluation of AEs during treatment and follow up • Changes in patient quality of life measured by HRQoL assessment EORTC QLQ – C30 provided in Georgian under license from EORTC
Exploratory: • Biomarker testing	• Testing of germline DNA in single blood sample at Day 0 for biomarker assessment. Testing of historic tumour biopsy material where available.

3 SELECTION CRITERIA

The study will enroll patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) after failure of at least one prior chemotherapeutic regimen.

3.1 Inclusion Criteria

- Diagnosis of Stage IIIB or Stage IV adenocarcinoma of the lung. Patients with mixed histology will be eligible if adenocarcinoma is the predominant histology.
- Prior chemotherapy for relapsed or metastatic NSCLC.
- Measurable disease according to RECIST version 1.1.
- Age≥18years.
- Life expectancy of at least 3 months.
- Negative human chorionic gonadotropin (hCG) test in women of childbearing potential (defined as women ≤ 50 years of age or history of amenorrhea for ≤ 12 months prior to study screening). Sexually active male and female patients of childbearing potential must agree to use an effective method of birth control e.g. barrier methods with spermicides, oral or parenteral contraceptives and/or intrauterine devices, during the entire duration of the study and for 1 month after the final administration of VAL401. Note that female patients may be surgically sterile (with appropriate documentation in the patient's medical records).
- Ability to give written, informed consent prior to any study-specific screening procedures with the understanding that the consent may be withdrawn by the patient at any time without prejudice.
- Patient is capable of understanding the protocol requirements, is willing and able to comply with the study protocol procedures, and has signed the informed consent document.

3.2 Exclusion Criteria

- Radiotherapy or surgery (other than biopsy) within 4 weeks prior to Cycle 1 Day 1.
- Any chemotherapy regimens (including investigational agents) with delayed toxicity with 6 weeks of Cycle 1 Day 1, or received any chemotherapy regimens given continuously or on a weekly basis which have limited potential for delayed toxicity within 2 weeks prior to Cycle 1 Day 1. Palliative treatment regimens, and other concomitant drugs regimens are permitted with stable toxicity, and recording of all concomitant medications (including herbal).
- Pregnant or lactating female patients.
- Active hepatitis B or C or other active liver disease (other than malignancy).
- Any active, clinically significant, viral, bacterial, or systemic fungal infection within 2 weeks prior to Cycle 1 Day 1; other than CMV which may be present providing any required concomitant anti-viral treatment is recorded appropriately.
- Known human immunodeficiency virus positivity.
- History of clinically significant cardiac condition, including ischemic cardiac event, myocardial infarction or unstable cardiac disease with 3 months prior to Cycle 1 Day 1.
- Active brain metastases (defined as stable for <4 weeks and/or symptomatic and/or requiring treatment with anticonvulsants or steroids and/or leptomeningeal disease).
- Any known contraindications to Risperidone or patients who would not be eligible to receive the treatment as defined in the Special Warnings and Precautions section of the local label for Risperidone.
- Any medical history that in the Investigator's opinion would jeopardise compliance with the protocol.

3.3 Patient Withdrawal or Discontinuation

Patients may withdraw from the study at any time without stating a reason and without prejudice to further treatment. A Final Study Visit should be performed 30 +/-3 days after the last dose of VAL401 to enable follow up safety assessments and further tumour assessment where required.

The Investigator may withdraw a patient from the study and discontinue study treatment and assessments at any time. Patients may be replaced if they withdraw prior to completion of Cycle 1, unless the reason for withdrawal is a toxicity related to treatment with VAL401, in order to evaluate tolerability and possible DLT. Example reasons for discontinuing a patient from this study are:

- Disease progression.
- The patient experiences a toxicity, where the re-introduction of VAL401 (including a dose reduction of VAL401), is not considered suitable. Exceptions may be considered where the toxicity is not considered to be VAL401 treatment-related.
- Other toxicities or events, unrelated to VAL401, that would, in the Investigator's opinion, prevent the patient from continuing on this trial.
- Protocol non-compliance. (All documentation concerning the patient must be as complete as possible. Withdrawals due to non-attendance of study visits must be followed-up by the Investigator to obtain the reason for where possible).
- Patient withdraws consent to participate in the study.

The Sponsor reserves the right to request the withdrawal of a patient due to protocol violation or other significant reason. Patients who experience a toxicity event which qualifies as a DLT, may continue to receive VAL401 if considered safe to do so and where continued treatment is considered by the Investigator to be in the patient's best interests. The decision to continue treatment may involve an adjustment (de-escalation) in dose or dose schedule.

3.4 Replacement of Withdrawn Patients

If a patient is withdrawn from the study for reasons other than a DLT-associated event before the end of the first treatment cycle during the dose escalation portion of the study, the patient will be replaced. Patients who withdraw from the study or discontinue treatment after completion of the first treatment cycle will not be replaced.

3.5 Procedures for Discontinuation

If a patient withdraws from the study prior to completion of Cycle 6, the reason for withdrawal should be sought and recorded in the patient file and the Case Report Form (CRF). Every effort will be made to complete the Final Study Visit.

3.6 Study or Site Termination

If the Sponsor or their representatives, Investigator, or Competent Authority officials discover conditions during the study that indicate that the study or site involvement should be terminated, this action may be taken after appropriate consultation with the Sponsor and the Investigator. Conditions that may warrant termination of the study or involvement of a study site include, but are not limited to:

- The discovery of an unexpected, serious, unacceptable risk to patients enrolled in the study.
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the study drug.
- Failure of the Investigator(s) to comply with pertinent clinical trial regulations.

- Submission of knowingly false information from the research facility to the Sponsor, study monitor, or Competent Authority.
- Insufficient adherence to protocol requirements.

Study termination and follow-up will be performed in accordance with applicable local regulations.

4 INVESTIGATIONAL PLAN

4.1 Study Design

This is a Phase II, open label study to assess the efficacy, safety and tolerability of VAL401 in the treatment of patients with locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) after failure of at least one prior chemotherapeutic regimen. Eligible patients will be enrolled as a single cohort and treated with VAL401, given as oral capsules.

Each patient will be dosed in 28 day cycles according to the schedule of: Cycle 1 Day 1: 2 mg in a single daily dose; Cycle 1 Day 2: 4 mg in a single daily dose; Cycle 1 Day 3: 6 mg in a single daily dose; Cycle 1 Day 4: 8 mg in a single daily dose; Cycle 1 Day 5 and onwards: 10 mg in a single daily dose. Cycles 2 – 6 each patient will receive a single daily dose of 10 mg (or their personal MTD if established).

If a patient experiences a DLT, the dose will be reduced to the previous acceptable dose, and the patient will remain on this personal MTD for the remainder of the study.

VAL401 is supplied as 5 mg and 1 mg dose capsules, each day's individual dose composed of the relevant combination of 1 mg and 5 mg capsules to total the required level.

All patients will remain on 10 mg as a single daily dose (or their personal MTD if reached) until they experience disease progression or unacceptable toxicity or until completion of 6 x 28 days cycles.

Patients will visit the study sites on each dosing day during the dose escalation period of Cycle 1 and then fortnightly at a minimum for a physical examination, recording of AEs and monitoring of quality of life by HRQoL questionnaires. Laboratory screens will be assessed at visits as indicated in the schedule, being Cycle 1 Day 5 (final day of dose escalation), Day 15 of all Cycles, Day 1 of Cycles 2 – 6 and at the Screening visit. Tumour assessment, including imaging (CT scan or other appropriate scan) where relevant, will be assessed in all patients at Screening and after every 3 cycles of treatment. Follow up assessments during the main study (Cycle 1-6) will be conducted in accordance with RECIST 1.1 (Eisenhauer 2009).

The majority of VAL401 doses will be self-administered by the patient at home, with the investigator supplying sufficient capsules to the patient at each visit to maintain dosing until the next site visit. The Investigator must stress to the patient the importance of reporting any deviations from protocol during home-dosing and encourage the patient to immediately report any potential AEs to the Investigator even if a visit is not due.

A full PK profile will be taken after the first dose of VAL401 and on Cycle 1 Day 15.

Patients will be asked to provide consent for access to archived tumour tissue, and blood samples and fresh biopsies will be taken (where possible) to allow for potential biomarker and PD assessment.

Patients whose disease has not progressed and who have not been withdrawn from therapy due to toxicity are eligible to continue receiving additional cycles of VAL401. For the purposes of this study, a full treatment course of VAL401 will considered to be 6 cycles. However, patients who respond to VAL401 treatment during the trial may have extended treatment with the Investigational Medicinal Product (IMP) where recommended by the investigator. Such patients will continue to be followed up for safety and continued response (see Schedule of Study Assessments). Patients receiving treatment beyond Cycle 6 may continue to be treated and followed up as part of this protocol, or be transferred to an extended treatment protocol.

4.2 Dose Escalation Scheme and DLT Evaluation

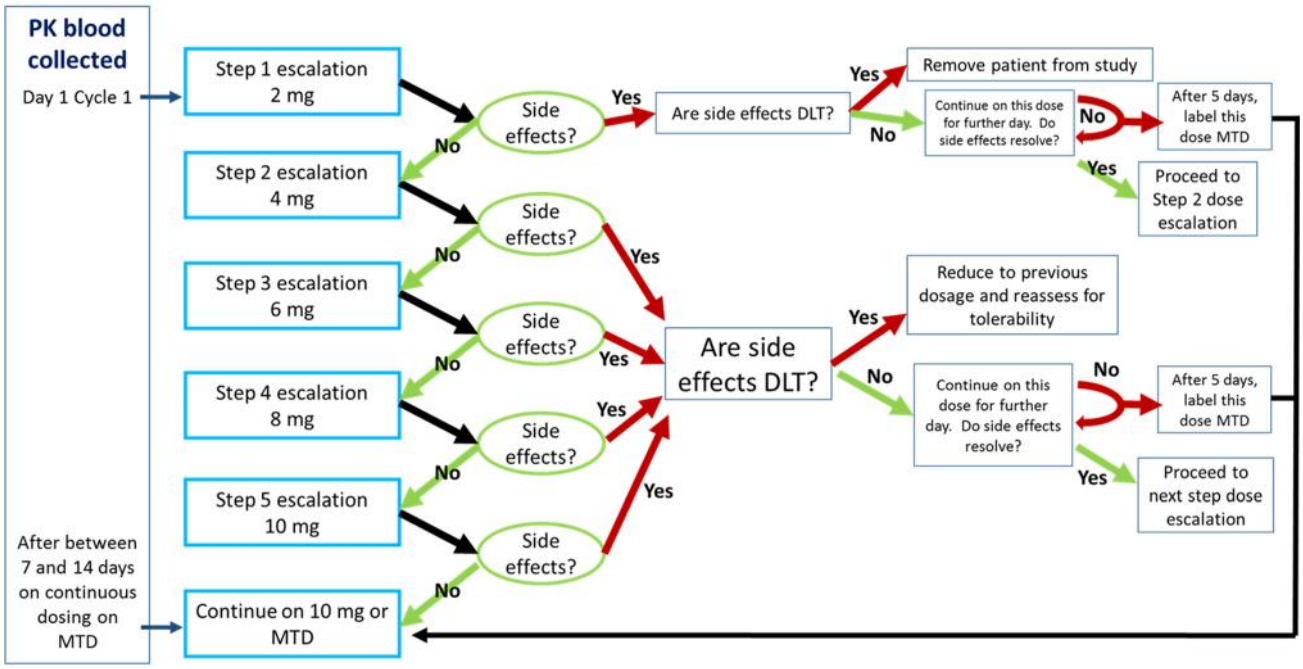
4.2.1 Dose Escalation

During Cycle 1 of treatment the following escalation steps are recommended in the absence of VAL401-related events which would lead to a more cautious dose escalation:

Cycle 1; Day	Daily Dose	Capsules administered
1	2 mg	2 x 1 mg
2	4 mg	4 x 1 mg
3	6 mg	1 x 5 mg + 1 x 1 mg
4	8 mg	1 x 5 mg + 3 x 1 mg
5 and subsequent	10 mg	2 x 5 mg

In the case where a potentially significant toxicity which is not a DLT, or a trend in toxicities seen, considered to be related to treatment with VAL401 occur and are considered to be a precursor of a clinically significant toxicity event; subsequent dose escalation steps *in that patient* may be more conservative (1mg per day increase until MTD reached, or a 24 hour delay until the next dose increase – at the discretion of the Investigator). This restriction may be reversed where there is no suggestion of a potentially clinical significant toxicity in the subsequent dose level.

Where a patient establishes a DLT, the dose should be reduced by one step, and the patient continued on this dose for the remainder of the study providing that the DLT has been resolved. This dose will be noted as the patient's personal MTD. The Schema below details the process for dose escalation decisions.



4.2.2 Dose Limiting Toxicity

The maximum feasible dose which may be administered is 10 mg per day. Should this dose be reached without the need to de-escalate the dose due to DLT, it will be termed the Maximum Administered Dose (MAD).

Safety Evaluations will be conducted daily during the dose escalation period (a minimum of Day 1 – Day 5 of Cycle 1), weekly for the remainder of cycle 1, and fortnightly thereafter. All events and suspected DLTs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

A DLT is defined as a VAL401-related Grade 3 or 4 adverse event that, in the opinion of the Investigator represents a clinically significant hazard to the subject, with the following **exceptions** as considered appropriate:

- Grade 3 or 4 laboratory abnormalities, which resolve spontaneously or can be corrected with appropriate treatment (such as electrolytes). For example, an event returns to baseline or to Grade 1 at the next assessment.
- Symptomatic adverse events, such as nausea, vomiting and diarrhea, if they can be reduced to less than Grade 3 with standard supportive measures, such as anti-emetics and anti-diarrhoeals within 72 hours.

Qualifying toxicity events must be considered to be clinically relevant e.g. in duration, and likely to be related to treatment with VAL401. DLT events will also be considered in terms of what is considered to be an appropriate next escalation step: in the case where the Investigator considers a daily escalation of 1 mg instead of 2 mg per day in the dose escalation period of Cycle 1, the toxicity of concern should be declared a DLT.

4.3 Dose Adjustments or Delays

In the case where a potentially significant toxicity which is not a DLT, or a trend in toxicities seen, considered to be related to treatment with VAL401 occur and are considered to be a precursor of a clinically significant toxicity event; subsequent dose escalation steps *in that patient* may be more conservative (1mg per day increase until MTD reached, or a 24 hour delay until the next dose increase – at the discretion of the Investigator). This restriction may be reversed where there is no suggestion of a potentially clinical significant toxicity in the subsequent dose level.

In the case where a DLT is observed the dose should be reduced to a prior acceptable level and maintained at that level providing that the DLT resolves. After resolution of the DLT the Investigator may propose a further increase in dose if they have reason to believe the patient would benefit from a slower dose escalation to provide an eventual higher MTD. Any attempted dose increase in this scenario is at the discretion of the Investigator and noted on the CRF.

If a dose is missed the patient should take the next dose on schedule and should not try to catch up the missed dose by taking double. If two or more consecutive doses are missed, the patient must re-escalate to their MTD, starting again at 2 mg per day.

4.4 Dose Reduction

The Sponsor may advise on a dose reduction step based on safety and on-going data evaluation from early enrolled patients. Intra-patient dose reduction of VAL401 is also permitted in this study. Investigators may choose to administer a lower dose which has previously been assessed during the

trial (or intermediate dose), to an individual patient based on safety evaluation of either the individual patient or other patients in the study.

Note that this approval may be expedited at any time if the Sponsor or Investigator receive information that is pertinent to patient welfare. All intra-patient dose reductions must be justified in writing as a preferable option over patient withdrawal.

5 STUDY SCHEDULE

Patients will attend the clinic for Screening assessments up to 28 days before receiving the first dose of VAL401.

Patients will be closely monitored after receiving their first dose of VAL401 and remain in the hospital clinic overnight for observation until the final PK sample is taken 24 hours after the initial dose; the second dose is administered, and all Day 2 study assessments have been completed. The study will commence with a dosing schedule of VAL401 given orally as a capsule (or combination of capsules) according to the dose escalation in Cycle 1 and then all on all days of a four week cycle. The majority of VAL401 doses will be self-administered by the patient at home, with the investigator supplying sufficient capsules to the patient at each visit to maintain dosing until the next site visit.

A tolerance of +/-1 day will be permissible for all study visits, except the dose escalation Cycle 1 visits which have no tolerance permitted and except the final study visit, which will have a tolerance of +/-3 days (this does not take into account any required dose delays). A tolerance of -1 day is permitted for all assessments relative to the study visit, unless specified otherwise (see footnotes to Schedule of Study Assessments).

Additional assessments may be conducted as clinically indicated.

5.1 Schedule of Study Assessments

Please also refer to the Schedule of Study Assessments tables and their associated footnotes. Below is a summary of study assessments described by visit.

Cycle 1, Screening (up to 28 days prior to Cycle 1, Day 1)

- ~ Informed consent (includes consent to obtain archived biopsy sample and for fresh biopsy samples where possible)
- ~ Demographics
- ~ Medical history (including tumour biomarker characteristics if known – for example EGFR mutant)
- ~ Concomitant medication
- ~ Inclusion/exclusion checks
- ~ ECOG Performance Status
- ~ Full physical examination (including height and weight)
- ~ Vital signs
- ~ ECG (resting 12-lead)
- ~ Clinical Chemistry
- ~ Haematology
- ~ Coagulation
- ~ Urinalysis
- ~ Virology to test for HBV, HCV, HIV, CMV IgG IgM
- ~ Serum pregnancy test (if applicable)
- ~ Tumour assessment (include historical information and Screening scans)
- ~ Biomarker testing – blood sample to obtain germ-line DNA
- ~ Health-related Quality of Life Questionnaire

Cycle 1, Day 1

- ~ Full physical examination
- ~ Vital signs (pre-dose and after VAL401 administration)

- ~ ECG (resting 12-lead) (taken in triplicate; pre-dose and up to 1 hour after VAL401 administration)
- ~ Urinalysis (include urine pregnancy test if applicable; no need to retest if within 7 days of last evaluation)
- ~ Adverse events
- ~ Concomitant medication
- ~ VAL401 administration
- ~ PK profile
- ~ Health-related Quality of Life Questionnaire

Cycle 1, Day 2

- ~ Full physical examination
- ~ Vital signs (pre-dose and after VAL401 administration)
- ~ ECG (resting 12-lead) (taken in triplicate; pre-dose and up to 1 hour after VAL401 administration)
- ~ Adverse events
- ~ Concomitant medication
- ~ VAL401 administration

Cycle 1, Day 3

- ~ Full physical examination
- ~ Vital signs (pre-dose and after VAL401 administration)
- ~ ECG (resting 12-lead) (taken in triplicate; pre-dose and up to 1 hour after VAL401 administration)
- ~ Adverse events
- ~ Concomitant medication
- ~ VAL401 administration

Cycle 1, Day 4

- ~ Full physical examination
- ~ Vital signs (pre-dose and after VAL401 administration)
- ~ ECG (resting 12-lead) (taken in triplicate; pre-dose and up to 1 hour after VAL401 administration)
- ~ Adverse events
- ~ Concomitant medication
- ~ VAL401 administration

Cycle 1, Day 5

- ~ Full physical examination
- ~ Vital signs (pre-dose and after VAL401 administration)
- ~ ECG (resting 12-lead) (taken in triplicate; pre-dose and up to 1 hour after VAL401 administration)
- ~ Adverse events
- ~ Concomitant medication
- ~ VAL401 administration
- ~ Clinical Chemistry
- ~ Haematology
- ~ Coagulation

Cycle 1, Day 15

- ~ Concomitant medication

- ~ ECOG Performance Status
- ~ Full physical examination (including height and weight)
- ~ Vital signs
- ~ ECG (resting 12-lead)
- ~ Adverse events
- ~ Clinical Chemistry
- ~ Haematology
- ~ Coagulation
- ~ VAL401 administration
- ~ PK profile
- ~ Health-related Quality of Life Questionnaire

Cycle 1, Day 29/Cycles 2-6, Day 1

- ~ Concomitant medication
- ~ ECOG Performance Status
- ~ Full physical examination (including height and weight)
- ~ Vital signs
- ~ ECG (resting 12-lead)
- ~ Adverse events
- ~ Clinical Chemistry
- ~ Haematology
- ~ Coagulation
- ~ Urinalysis (include urine pregnancy test if applicable)
- ~ VAL401 administration
- ~ Health-related Quality of Life Questionnaire

Cycles 2-6, Day 15

- ~ Concomitant medication
- ~ ECOG Performance Status
- ~ Full physical examination (including height and weight)
- ~ Vital signs
- ~ ECG (resting 12-lead)
- ~ Adverse events
- ~ Clinical Chemistry
- ~ Haematology
- ~ Coagulation
- ~ VAL401 administration
- ~ Health-related Quality of Life Questionnaire

Final Study Visit (to be performed 30 days (±3 days) after the last dose of VAL401)

- ~ Concomitant medication
- ~ ECOG Performance Status
- ~ Full physical examination (including height and weight)
- ~ Vital signs
- ~ ECG (resting 12-lead)
- ~ Adverse events
- ~ Clinical Chemistry
- ~ Haematology
- ~ Coagulation
- ~ Urinalysis (include urine pregnancy test if applicable)

~ Health-related Quality of Life Questionnaire

Tumour assessment should be carried out after every 3 cycles, at a visit deemed convenient to the patient and Investigator at any time within the relevant cycle. If disease progression is suspected, tumour assessment may be carried out earlier than scheduled.

Where a patient continues VAL401 treatment beyond Cycle 6, the following assessments should be carried out on the final day of each cycle, and the patient supplied with a full subsequent cycle of VAL401 capsules:

Cycles 7 and beyond, Day 28

~ Concomitant medication
~ ECOG Performance Status
~ Full physical examination (including height and weight)
~ Vital signs
~ ECG (resting 12-lead)
~ Adverse events
~ Health-related Quality of Life Questionnaire

5.2 Volume of Blood Sampling

Based on the unit blood volumes given for each study assessment, it is anticipated that patients enrolled to the dose escalation portion of the study will have a maximum of 420 mL of blood drawn if they complete all 6 cycles of treatment and the final study visit (including potential for repeat analysis as clinical required), and have the maximum number of blood samples taken for PK and biomarker assessment. Those patients who only complete Cycle 1 plus the final study visit, would have a maximum of 308 mL blood drawn (including potential for repeat analysis as clinically required).

Duration on trial	**Volume of blood drawn**
Screening, Cycle 1 and Final Visit	154 mL (assumes maximum samples taken)
Screening, Cycles 1 – 6 and Final Visit	264 mL (assumes maximum samples taken)
Notes	
PK – assuming all 20 samples are taken	100 mL
Clinical Chemistry – assuming all 14 samples taken	70 mL
Haematology (including coagulation) – assuming all 14 samples taken	84 mL
Biomarker	10 mL

The volume of blood drawn for each patient will also be described in the Patient Information Sheet. Efforts will be made to reduce the number of PK samples to be taken upon evaluation of cohort data during the trial.

5.3 Description of Study Assessments

5.3.1 Adverse Events

Adverse events (AEs) will be captured from the time the patient gives consent until the 30 day follow-up (Final Study Visit). There will be a baseline medical condition review taken at screening. AEs, other than the primary disease under evaluation, that worsen in severity or frequency from this baseline assessment during the study, should be recorded and reported as AEs.

AEs will be graded according to the NCI CTCAE v4.03 for cancer clinical trials (Appendix B). For events not addressed in the CTCAE v4.03, the alternative severity classifications provided in Section

7.4.1 apply.

AEs should continue to be captured for a further 30 days from the end of the last dose administration of VAL401. On-going SAEs will be followed up until considered resolved; returns to baseline; is chronically ongoing or explained by the Principal Investigator.

Symptoms and signs of exacerbation or worsening of the patient's primary disease will not be captured as AEs. For the purpose of data capture, disease progression as evaluated by RECIST1.1, will not be considered to be an AE and will be captured in the Tumour Assessment CRF modules.

5.3.2 Laboratory safety measurements

Blood and urine samples for determination of clinical chemistry, haematology, coagulation and urinalysis parameters will be taken at the times given in the Schedule of Study Assessments and as clinically indicated. The date and time of collection will be recorded in the source data and on the CRF.

Clinical chemistry, haematology, coagulation analysis and urinalysis will be performed at each site's local laboratory or other local laboratories as appropriate. The required blood volume for clinical chemistry samples is 5 mL and 6 mL for haematology (including coagulation).

Copies of laboratory accreditation certificates and reference ranges will be provided prior to the analysis of the first patient sample.

The laboratory variables to be measured are described in Appendix C.

5.3.3 Resting 12-lead electrocardiogram (ECG)

For timing of individual measurements refer to Schedule of Study Assessments.

All 12-lead Electrocardiograms (ECGs) should be recorded while the patient is in the supine position. ECGs taken on Cycle 1 Days 1 – 5 (the dose escalation period) will be assessed in triplicate at pre-dose and up to 1 hour after VAL401 administration. ECGs taken in other site visits may be taken irrespective of VAL401 timing of dosing. The Investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected.

ECGs will be recorded at 25 mm/sec. All efforts should be made to ensure that an identical ECG machine is used to collect traces for individual patients. If any clinically significant findings are observed on the ECG, the Investigator will record it as an AE where the finding represents a clinically significant change from the baseline assessment taken at screening.

5.3.4 Vital signs

For the timing of individual measurements, refer to the Schedule of Study Assessments. The date and time of collection and measurement will be recorded on the appropriate CRF.

Measurements of heart rate, axillary temperature, blood pressure and respiratory rate will be made after the patient has been resting supine for a minimum of 5 minutes. Patients will be closely monitored during and for up to 1 hour following their first VAL401 administration (Cycle 1, Day 1).

5.3.5 Pharmacokinetic assessments

Blood samples will be drawn for the determination of VAL401 concentration-time profiles in serum.

- Cycle 1, Day 1: pre-dose (0h) then 10, 15, 30 min, 1, 2, 4, 8, 10 and 24 h post-administration.
- Cycle 1, Day 15: pre-dose (0h) then 10, 15, 30 min, 1, 2, 4, 8, 10 and 24 h post-administration.

Note that the ability to take the latter PK samples in a PK profile dosing day will be dependent on the local site operational procedures.

Nominal PK blood sampling times should be adhered to as closely as possible. It is essential that the actual time and date of collection of each blood sample be recorded in the patient's records and in the CRF.

The volume of blood to be collected per sample should be 5 mL.

This measurement will be performed by a central laboratory. Full instructions for blood sample preparation, aliquoting of samples, sample storage and shipping details will be provided.

5.3.6 Tumour assessment

Tumour assessment during the main part of the study (Cycles 1-6) will follow the RECIST1.1 guidelines.

Assessment will include, as appropriate, the assessment of measurable and any selected non-measurable lesions by CT scan of chest, abdomen and pelvis at Screening and on the completion of every 3 cycles. Other assessments e.g. whole body MRI may be assessed as requested by Investigator.

Additional scans may be performed to confirm a Complete Response or Partial Response or disease progression. Other assessments e.g. whole body MRI may be assessed as requested by Investigator. Patients on study after 6 cycles will have tumour assessment every 3 – 6 cycles depending standard local clinical practice.

Note that magnetic resonance imaging (MRI) may be used in the event CT is not available, but for each patient, the radiographic measurement used at Screening/Baseline (i.e., CT or MRI) must be used serially throughout the duration of study participation.
Early stage antitumour response evaluations should also take into account the guidelines for the evaluation of immune therapy activity in solid tumors which describes an immune-related response criteria (Wolchok, et al. 2009).

5.3.7 Biomarker testing

Patients will be asked to provide consent for access to archived tumour tissue (FFPE sections) for potential future analysis of biomarkers including possible evaluation tumour cell DNA. Where a rationale for a specific biomarker assessment has been identified, this consent will allow archived tumour biopsy material to be tested for this purpose. A 10 mL blood sample will also be taken at Screening for collection of germ-line DNA.

6 STUDY MEDICATION AND ADMINISTRATION

6.1 Study Medication

The Quality Control Standards and requirements for VAL401 study medication are described in separate release protocols/Certificate of Analysis.

ValiSeek will supply VAL401 as capsules containing either 5 mg or 1 mg VAL401 in lipid excipients.

Composition of VAL401 capsules:

Active Component	Risperidone, 5 mg or 1 mg
Excipients	Rumenic Acid, [redacted]
Stability	[redacted]
Storage and Handling	[redacted]
Excipients of human or animal origin	Hard Gelatin capsule shells

6.2 Selection of Doses in the Study and Duration of Treatment

The starting dose level of VAL401 is 2 mg as a single daily dose on Cycle 1 Day 1, with escalation of 2 mg per day to a maximum of 10 mg per day such that Cycle 1 Day 2 provides 4 mg VAL401 as a single daily dose, Day 3: 6 mg, Day 4: 8 mg, Day 5 and all subsequent days 10 mg as a single daily dose.

A treatment cycle is considered as 28 days from (and including) the first day of dosing. Those patients who show an improvement or stable disease during treatment in the absence of DLT may receive up to 6 continuous cycles of therapy which is considered to be a complete treatment course for the purposes of this clinical trial. Patients may be permitted to receive more than 6 cycles of VAL401 where their cancer has not progressed on study and their investigator recommends this course of action.

6.3 Packaging and Labelling

Clinical trial supplies will be provided as screw top bottles containing VAL401 capsules. Separate bottles will be supplied containing either 18 x 5 mg VAL401 capsules or 18 x 1 mg VAL401 capsules.

All vials and secondary packaging will be labelled for the purpose of the clinical trial in accordance with applicable regulatory requirements.

6.4 VAL401 Administration

The maximum dose for any single dose of VAL401 will not exceed 10 mg (2 x 5 mg capsules).

The majority of VAL401 dose administrations (after the dose escalation schedule) will be achieved in the patient's home, and not during site visits. The patient should be encouraged to consider an appropriate time of day to take the dose, in particular if a patient experiences mild sedation immediately after dosing, the Investigator should recommend evening dosing in order that the sedation is resolved before morning waking.

VAL401 oral capsules should be taken on an empty stomach – either a minimum of 30 minutes before food or a minimum of 1 hour after food.

VAL401 capsules must be swallowed whole, patients should be directed not to break open the capsule.

6.5 Storage

The capsules should remain in the screw-top bottles as supplied and stored in refrigerated storage (2 – 8 ^{o}C). The Investigator should ensure the patient has sufficient supplies of capsules to complete the administration required prior to the next patient visit.

6.6 Replacement of Medication

Sufficient doses of medication will be supplied. In case the supplies are broken or unusable, they should be replaced. Although the Sponsor need not be notified immediately in these cases, documentation of the use and/or loss of any vial must be recorded by the pharmacist on the medication accountability form.

6.7 Accountability

The Investigator is obliged to keep sufficient documentation of the delivery, use and destruction or return of unused, used or partially used IMP. The documentation must include dates, quantities, patient numbers, batch numbers or other identification number. The Investigator may assign some or all of the Investigator's duties for drug accountability to an appropriate pharmacist. Roles and responsibilities of site staff will be recorded in the Trial Master File.

The Investigator should maintain records that document adequately that the patients were administered the doses specified in the protocol and reconcile all VAL401 IMP received for the trial. The local study monitor will be responsible for checking the drug accountability records maintained by the site during the monitoring visits.

The medication provided for this study is for use only as directed in the protocol. It is the Investigator/Institution's responsibility to establish a system for handling study drug so as to ensure that:

- deliveries of VAL401 are correctly received by a responsible person;
- such deliveries are recorded;
- study treatments are handled and stored safely and properly as stated on the label;
- study drug is only dispensed to study patients in accordance with the protocol; and
- any unused study drug is destroyed locally or returned for destruction in liaison with the study monitor.

Throughout the study, it must be possible to reconcile delivery records with records of usage and any destroyed/returned stock. Records of usage should include the identification of the patient to whom the study treatment was dispensed and the quantity and date of dispensing. This record is in addition to any drug accountability information recorded on the CRF. Any discrepancies must be accounted for on the appropriate forms.

The return or destruction of unused drug will be conducted after written approval by the Sponsor, with appropriate documentation and drug accountability procedures completed following destruction.

6.8 Treatment Allocation

In order to ensure that the appropriate numbers of patients are enrolled; on identifying a potential study patient, the Investigator is required to complete a patient registration request form confirming patient eligibility and requesting a place on the study. Where appropriate, sites will then receive a confirmation of enrolment form confirming the enrolment of the patient. Patients must not be enrolled until this confirmation is received. There will be regular communication with study sites during the trial to ensure Investigators are aware of enrolment status on the trial and suitable times for patient enrolment.

6.9 Blinding and Procedures for Un-Blinding the Study

This is an open-label study and there are no blinding or un-blinding procedures.

6.10 Permitted and Restricted Concomitant Medications/Treatments

All prescription, non-prescription, or over-the-counter medications (including herbal remedies) given to, or taken by the patient at study entry (including Screening) and during the study must be clearly documented on the CRF.

Any medication considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator(s).

For treatment of DLT or any other clinically significant events, any available standard therapy may be used as required. In the case of anemia, transfusions with pRBC can be administered.

Prohibited treatments are summarized below:

- No other antineoplastic agents will be permitted to be initiated during this study (patients on stable, long term treatment of any form are permitted providing the medication is not contraindicated by the SmPC for Risperidone).
- No concurrent radiation treatment will be permitted during this study (except for palliative care e.g. for bone metastases).
- Herbal remedies unless pre-approved by the treating physician.

7 ADVERSE EVENTS AND REPORTING REQUIREMENTS

7.1 Assessment of Safety

All patients who receive treatment with VAL401 will be considered evaluable for safety. All AEs will be collected from the time the patient gives informed consent up to and including the 30 day follow up (Final Study Visit). There will be a baseline medical condition review taken at screening. AEs, other than the primary disease under evaluation, that worsen in severity or frequency from this baseline assessment during the study, should be recorded and reported as AEs. If the Investigator detects a serious adverse event in a study patient after the end of the period of observation and considers the event possibly related to prior study treatment or procedures, he or she should contact the sponsor to determine how the AE should be documented and reported.

7.2 Adverse Event Definition

An AE is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the IMP.

During clinical trials, AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient. To prevent reporting bias, patients should not be questioned regarding the specific occurrence of one or more AEs.

Adverse events include: (a) worsening (change in nature, severity, or frequency) of conditions present at the start of the study, (b) concurrent illness, (c) drug interactions, (d) experiences related or possibly related to concomitant medications, (e) clinically significant abnormal laboratory values or shifts from baseline, and (f) clinically significant abnormalities in physical examination, vital signs, weight, or electrocardiogram.

Progression of the disease under study will not be captured as an AE.

Surgical procedures or other therapeutic interventions themselves are not AEs, but the condition for which the surgery/intervention is required is an AE and should be documented accordingly.

Planned surgical measures and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the period of observation and did not worsen during study. In the latter case the condition should be reported as medical history.

7.3 Importance of Adverse Event Reporting

Timely and complete reporting of safety information assists ValiSeek and the Investigators in identifying any untoward medical occurrence, thereby allowing: (1) safety of study patients; (2) a greater understanding of the overall safety profile of the investigational drug; (3) recognition of dose-related investigational drug toxicity; (4) appropriate modification of study protocols; (5) improvements in study design or procedures; and (6) adherence to regulatory requirements.

7.4 Evaluating Adverse Events

Following the patient's written consent to participate in the study, all AEs should be collected. Following the baseline medical history assessment of the patient taken at screening, all identified AEs must be recorded and described on the appropriate AE page of the CRF. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The

following information should be captured for all AEs: date of onset and resolution, severity of the event (see definitions in Section 7.4.1), assessment whether the event was serious or non-serious (see definitions in Section 7.4.2), Investigator's opinion of the relationship to investigational drug (see definitions in Section 7.4.6), treatment required for the AE, action taken with IMP, and information regarding resolution/outcome.

7.4.1 Severity

All AEs (including SAEs) are to be accurately recorded on the AE page of the patient's CRF. Each event will be graded for severity using the classifications of CTCAE v4.03. For events not addressed in the CTCAE v4.03, classifications the following grading will apply:

- **Mild (Grade 1) –** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate (Grade 2) –** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activity of Daily Living (ADL).
- **Severe (Grade 3) –** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- **Life-threatening (Grade 4) –**Life-threatening consequences; urgent intervention indicated.
- **Death (Grade 5) –** related to AE.

7.4.2 Seriousness

A serious adverse event is any untoward medical occurrence that at any dose (including overdose):

- Results in death.
- Is life-threatening:
    - "Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization:
    - This means that hospital in-patient admission, or prolongation of hospital stay, were required for the treatment of the AE, or that they occurred as a consequence of the event.
    - Visits to a hospital by ambulance or to the emergency room without admission will not be regarded as hospitalization unless the event fulfills any other of the serious criteria.

- Results in persistent or significant disability or incapacity:
    - "Persistent or significant disability or incapacity" means a permanent or significant and substantial disruption of a person's ability to carry out normal life functions.
- Is a congenital anomaly or birth defect.
- Is an important medical event:

- Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.4.3 Pregnancy

In principle, pregnancy and the lactation period, or planning to father a child, are exclusion criteria for clinical studies involving investigational drugs. In the event of a pregnancy occurring during the course of this study, ValiSeek must be notified immediately. If the pregnancy involves a patient enrolled to the trial, the patient should be immediately withdrawn from study. The pregnant patient or the patient's partner should followed-up during the entire course of the pregnancy and postpartum period.

Parental and neonatal outcomes must be recorded even if they are completely normal and without AEs. Off-spring should be followed up for at least 8 weeks after delivery. Longer observation periods may be determined by the sponsor if an adverse outcome of the pregnancy was observed.

Pregnancies occurring during the study up to 90 days after the completion of the study drug must also be reported to ValiSeek Limited within one working day of becoming aware of them using a clinical trial pregnancy reporting form. When a "pregnancy is detected without an adverse outcome", the Investigator should only complete the SAE form and send this to the sponsor. It should be clearly stated that no AE was observed. In this case, there is no need to complete the "adverse event" page in the case report form.

7.4.4 Misuse and Overdose

Drug misuse and drug overdose should be reported in the same format and within the same timelines as a serious adverse event, even if they may not result in an adverse outcome.

Overdose is defined as any dose administration where >10% over the correct dose amount is administered whether or not associated with an AE.

For monitoring purposes, any case of overdose must be reported on an SAE form as per Section 7.6.

When an "overdose" or "drug misuse" of the investigational product occurs without an AE the Investigator should complete the SAE form as per section 7.6. It should be clearly stated that no AE was observed. In this case, there is no need to complete the "adverse event" page in the case report form

If the pharmacy discovers that an overdose has or may have been administered they should contact the Investigator and study coordinator.

7.4.5 Investigational Product Complaints

Pharmaceutical technical complaints associated with the investigational product must be reported to the sponsor immediately. The same reporting timelines as for serious adverse events apply.

7.4.6 Relationship

All AEs (including SAEs) will be assessed for the relationship of the AE to the study drug using the following definitions:

- Not/Unlikely Related

The AE is not related if exposure to the investigational product has not occurred, OR the occurrence of the AE is not reasonably related in time, OR the AE is considered unlikely to be related to use of the investigational product because there are no facts (evidence) or arguments to suggest a causal relationship AND there is a possible alternative explanation.

- Possibly Related

The administration of the investigational product and AE are considered reasonably related in time AND there are facts (evidence) or arguments to suggest a causal relationship. This does not exclude that the AE could be explained by causes other than exposure to the investigational product.*

- Probably Related

Exposure to the investigational product and AE are reasonably related in time AND the investigational product is more likely than other causes to be responsible for the AE, OR is the most likely cause of the AE.

- Definitely Related

There is a reasonable temporal sequence between exposure to the investigational product and the AE, OR the event follows a known or expected response pattern to the investigational product; AND is confirmed by improvement on stopping/ reducing the dosage of the investigational product. It may also be confirmed by reappearance upon repeated exposure where this is medically and ethically acceptable.

**For consideration of DLTs and subsequent dose escalation decisions, the likely causality of clinically significant AEs as defined in Section 4.2.1, must be carefully considered.*

The relationship of the study treatment to an AE will be determined by the Investigator and subsequently reviewed by the Medical Monitor.

For reporting and data analysis purposes, AEs reported with a causality assessment of "Definitely", "Probably" and "Possibly" are to be considered as "having a reasonable causal relationship" to study drug. In case of disagreement between the Investigator and the Sponsor's Medical Monitor the more conservative assessment will determine the reportability of the case.

7.5 Evaluating Dose Limiting Toxicities (DLTs)/Serious Adverse Events (SAEs)

DLTs, SAEs classified as DLTs and SAEs will be noted on the AE CRF and on a SAE form. This form will classify the event as a DLT only; SAE only; or DLT and SAE.

7.5.1 Unexpected adverse events

The Sponsor will assess all serious adverse events whether they are expected or unexpected. An unexpected adverse event is any adverse drug event, the outcome, specificity or severity of which is not consistent with those noted in the current IB or the SmPC for Risperidone.

7.6 Reporting DLTs/SAEs

Adverse events classified as DLTs and/or SAEs using the definitions above must be recorded on the SAE form.

The Principal Investigator (or designee) will complete the SAE form and e-mail (or fax if e-mail is not possible) this and any available supporting documentation of a Serious Adverse Reaction or Adverse Event to Clinical Accelerator, UK (CRO) and to ValiSeek Limited, UK (Sponsor) and the sponsor will notify the competent authorities.

The PI must announce AMDM about serious adverse events / serious unexpected adverse reactions in accordance with Annex 1 (pag. 129 pct. 13.4) MoH Order no. 10 of 14.01. 2002 and MoH Order no. 22 of 12.01.2006.

7.6.1 Reporting SAEs to the IRB or Ethics Committee and Regulatory Authorities

The Investigator must comply with the applicable local regulatory requirements related to the reporting of SAEs to the required Independent Ethics Committees (IEC). Other SAEs (i.e. expected or unrelated SAEs) should be reported per the relevant institution's procedures.

Until such time that an AE is included in the IB, it should be considered unexpected, regardless of whether the AE has been the subject of a previous Safety Update. All expectedness assessments will be made by the Sponsor.

All events qualifying as SUSARs will be reported to the relevant regulatory authorities according to local practices.

7.6.2 Follow-up information on an SAE

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g. hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report. The original SAE form must be kept on file at the study site. The sponsor will also review SAE reports for missing information and send queries to the site for resolution as appropriate.

Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out by the Principal

Investigator (or designee). An SAE is followed until it is considered resolved; returns to baseline; is chronically ongoing or explained by the Principal Investigator.

8 DATA EVALUATION: CRITERIA FOR EVALUATION OF OBJECTIVES

8.1 End of Study and Study Completion

End of study is defined as the last patient visit or study assessment. Study completion occurs upon final database lock and production of the main study report. Exceptions may be made in the case where a single patient, or limited number of patients, continue to receive VAL401 after 6 cycles of treatment. In such cases End of Study and Study Completion may be defined at a point when all patients have had the opportunity to complete 6 cycles of IMP. Additional data from the patient(s) continuing on treatment will be presented as an Addendum to the CSR upon cessation of treatment.

8.2 Statistical Considerations

Detailed statistical analysis information will be provided separately in the Statistical Analysis Plan (SAP). The SAP will detail all data handling rules, including the management of missing values and the handling of data for withdrawn patients. The SAP will also outline protocol violation criteria along with any specific analysis population definitions. Any deviations to the planned analyses specified or populations defined within the SAP will be justified in writing and presented within the final clinical study report.

The clinical database lock will occur after all data are reconciled (i.e. "cleaned") for all patients who participate. Database lock will occur on two occasions – a preliminary database will be generated from data collected during screening and up to and including the Cycle 1, Day 15 pharmacokinetic measurement when all patients have completed this section; the final database lock will occur after all patients have completed the final visit. A single clinical study report will be generated for this study. The SAP will be finalized and signed before the database lock.

8.3 Demographic and Other Baseline Characteristics

Demographic characteristics will be listed and summarized. Other baseline characteristics will only be listed.

8.4 Statistical Methods for Safety Parameters

All safety and tolerability assessments will be based on the safety analysis set, which is defined as all patients who have received at least one dose of study medication.

Results will be presented using descriptive statistics. Data collected at screening and up to and including the Pharmacokinetic measurements collected on Day 15 Cycle 1 will be analysed during a preliminary analysis point when all patients have reached this stage. Final analysis will correlate all remaining data with the preliminary set after last patient, last visit, all data is reconciled and the complete database is locked.

Vital signs, resting 12-lead ECGs, haematology, coagulation, clinical chemistry and urinalysis data will be listed by dose group and time-point.

The number and percent of patients experiencing one or more AEs will be summarized by dose level group, relationship to study drug, and severity. AEs will be coded using MedDRA terminology. AEs that have missing onset dates will be considered to be treatment-emergent, unless the stop date is known to be prior to the first administration of the study medication.

SAEs and DLTs will also be presented separately.

8.5 Statistical Methods for Pharmacokinetic Parameters

PK parameters will be estimated for each patient using a fully validated version of a recognized statistical software package. The following parameters will be derived, where appropriate, from the individual serum concentration versus time profiles of VAL401.

Parameter	Definition
C_{inf}	The observed concentration at the end of the administration.
C_{max}	The maximum observed concentration.
t_{max}	The time at which C_{max} was apparent.
AUC_{0-t}	The area under the concentration versus time curve from time zero to the sampling time at the last quantifiable concentration (C_t) at t_{last} (the time of the last quantifiable concentration) calculated by the linear trapezoidal rule.
λ_z	The apparent terminal rate constant, estimated using the negative slope of the least square regression analysis of the log concentration versus time data for the terminal linear portion of the curve.
$t_{½}$	The apparent terminal half-life, calculated from $Log_e\ 2 / \lambda_z$
$AUC_{0-\infty}$	The area under the concentration-time curve estimated from time zero to infinity as the sum of the two areas: AUC0-t and AUC_{extrap}, where AUC_{extrap} is calculated as C_t / λ_z.
CL	The systemic clearance calculated as: Dose/ AUC0-∞.
V_{ss}	The apparent volume of distribution at steady state calculated as: Dose/AUC x (AUMC/ $AUC_{0-\infty}$).

Additional PK parameters may be calculated as appropriate.

8.6 Evaluation of Tumour Response (all patients)

Tumour assessment during the main study (Cycles 1-6) will follow RECIST 1.1 (Eisenhauer, et al. 2009) and will include CT scans (or comparable appropriate scan). Tumour assessment beyond Cycle 6 will follow local practice.

Response rate will be summarised and a 95% CI calculated.

8.7 Estimated Sample Size

It is anticipated that up to 20 patients locally advanced or metastatic non-small cell lung cancer cancer may be enrolled in this study.

9 QUALITY ASSURANCE

9.1 Data Recording

All CRF data will be collected using a paper CRF system. All data will be entered into the CRF by the Site Staff. These data will then be source data verified and reviewed by the study monitor. All queries will be raised and resolved between the monitor and site.

After all queries have been resolved and any summary/analysis populations approved, the database will be locked and the data released for summary and analysis.

9.2 Study Monitoring

The assigned study monitor will review the progress of the study on a regular basis to ensure adequate and accurate data collections. Monitoring site visits to review CRFs, patient case notes, administrative documentation including the Investigator Site File and frequent telephone/e-mail communications with site will be performed throughout the study.

At each study monitoring visit the Investigator will make available all records pertaining to the study. To allow sufficient time to assemble documentation for the study monitor, monitoring visits will be confirmed in advance of planned visits.

9.3 Clinical Study Audit

The Sponsor, Sponsor representative or external regulatory agency may at any time during or after completion of the study conduct a GCP audit. Prior notice will be given to each site selected for audit in advance of a planned audit.

9.4 Clinical Study Report

The results of the study will be presented in an integrated clinical study report according to ICH guidelines.

9.5 Data Retention and Availability

The Investigator is required to maintain copies of all essential study documentation, including the Site Study File, all CRF data (including the full audit trail and all data queries), signed informed consent forms, and records for the receipt and disposition of study medications, for a period of at least five years after study completion, as specified by ICH GCP and longer if required by local or regulatory authorities.

During the study, the Investigator must make study data accessible to the study monitors, the Sponsor (or a third party auditor assigned by the Sponsor), and relevant IRB/IECs and regulatory agencies. A file for each patient must be maintained that includes the signed informed consent form and all source documentation related to that patient. The Investigator must ensure the availability of source documents from which the information in the CRF was derived.

10 ETHICS REVIEW/INFORMED CONSENT

The final study protocol and patient informed consent form will be approved by the appropriate independent ethics committee for each investigational site. Approval will be received in writing before initiation of the study.

Changes to the protocol during the trial will be documented as amendments. Depending on the contents of the amendment and local legal requirements, the amendment will be submitted for approval to the relevant ethics committees and to the relevant competent authorities prior to implementation. Exceptions are cases of changes made to protect patient safety, which will be implemented immediately.

If an amendment substantially alters the trial design, increases the potential risk to the patients, affects the treatment of the patient or might otherwise influence the willingness of the patient to participate in the trial, then the information sheet must be revised and submitted to the relevant ethics committees and, where necessary, to the relevant competent authorities, for review and approval. When a patient is currently undergoing trial procedures and is affected by the amendment, then the patient must be asked to consent again using the new information sheet.

10.1 Ethical Conduct of the Study

The study will be conducted in accordance with ICH GCP, the Declaration of Helsinki and the requirements of local regulatory authorities and ethics committees.

10.2 Informed Consent

The principles of informed consent in the Declaration of Helsinki and GCP Guidelines will be implemented before any protocol-specific procedures or interventions are carried out.

All patients will be informed that participation is voluntary and that they can cease participation at any time without necessarily giving a reason and without any penalty or loss of benefits to which they are entitled.

With the help of the information sheet the patient will be informed about the IMP and anticipated effects, and the reason, design and implication of the trial. The patient must give consent to participate prior to enrolment in the trial. This consent must be given in writing. The Investigator who conducts the informed consent discussion must also sign. The Investigator may delegate this responsibility to a suitably qualified member of the study team e.g. sub-investigator, if permitted by local regulations. This delegation of responsibility must be recorded in the study file. By giving signed consent, the patient will confirm that their participation is voluntary and that they will follow the instructions of the Investigator and answer the questions asked. Signatures must be personally dated.

The signed and dated consent form will be kept by the Investigator. Prior to participation in the trial, the patient should receive a copy of the signed and dated written informed consent form.

The consent form and information sheet must include all elements required by law, local regulations, GCP and ICH guidelines including consent to allow the Sponsor, Sponsor representative or external

regulatory auditor to review the patient's medical records. This gives permission to examine, analyze, verify and reproduce any records and reports that are important to the evaluation of the trial.

Any party with direct access must take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of the patient's identities and Sponsor's proprietary information. It is the study monitor's responsibility to verify that each patient has consented, in writing, to direct access.

10.3 Insurance

Insurance for the patients participating in this trial will be arranged by ValiSeek, as Sponsor of the clinical trial, in accordance with the regulatory requirements of the countries involved. A copy of the country-specific insurance certificates will be held in the Trial Master File and in the Investigator site file.

11 PUBLICATION POLICY

The original CRFs and all data generated during the clinical study using the given protocol will become the property of the Sponsor.

Any proposed publication or presentation (including a manuscript, abstract or poster) for submission to a journal or scientific meeting should be sent to the Sponsor for review at least one month prior to submission. No single centre or groups of centres may publish individually. Publications arising from this clinical study will include all Investigators and Sponsor representatives as authors. The Sponsor's comments on the proposed publication shall be considered in good faith by the authors. The Sponsor may delay such submission by a maximum of ninety (90) days if it reasonably believes that publication of results may compromise its intellectual property rights, or else require that such information or data are removed from the proposed publication. Publication of the results will not include confidential information without the permission of the Sponsor. Approval of such requests to submit for publication will not be unreasonably withheld.

The Sponsor may announce quality assured summary data in order to comply with Financial Regulatory Authorities, whilst ensuring, so far as possible, that such announcements will not compromise the Investigators ability to publish the data in appropriate scientific forums.

This publication policy will be reviewed to ensure compliance with the anticipated changes in EU and Georgian legislation in 2016.

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APPENDIX A: ECOG PERFORMANCE STATUS

Eastern Co-operative Oncology Group (ECOG) Performance Status

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

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APPENDIX B: NCI CTCAE v4.03

A complete copy of the NCI CTCAE v4.03 will be held in each Site Study File.

Please use link below to access most current version of the NCI CTCAE.
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 .

APPENDIX C: LOCAL LABORATORY PARAMETERS

Clinical chemistry	Haematology, including coagulation screen	Urinalysis
Calcium	Red cell count	Glucose
Total protein	Hemoglobin	Protein
Albumin	Hematocrit	Bilirubin
Total bilirubin	Absolute reticulocyte count	Ketones
Alanine transaminase (ALT, SGPT)	Platelet count	Blood
Aspartate transaminase (AST, SGOT)	White blood cells	pH
Alkaline phosphatase	Leucocyte differential count (% & absolute)	Pregnancy test as required
Glucose (random)	International normalized ratio or prothrombin time	
Sodium	Activated partial thromboplastin time	
Potassium		
Bicarbonate		
Chloride		
Magnesium		
Urea		
Creatinine		
Phosphate		
Uric acid		
Pregnancy test as required		