CLINICAL STUDY PROTOCOL

A Phase I/II, Dose Escalation Study to Assess the Safety and Tolerability of VAL201 in Patients with Locally Advanced or Metastatic Prostate Cancer and Other Advanced Solid Tumours

Protocol No: VAL201-001

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PROTOCOL SYNOPSIS

Protocol No:
VAL201-001

Study Title:
A Phase I/II, Dose Escalation Study to Assess the Safety and Tolerability of VAL201 in Patients with Locally Advanced or Metastatic Prostate Cancer and other Advanced Solid Tumours

Investigational Product:
VAL201. VAL201 is a synthetic decapeptide, designed to inhibit the interaction of the androgen receptor (AR) or estradiol receptor (ER) with the kinase Src.

Phase of Development:
I/II

No of Sites:
For dose escalation: up to 3

For further assessment of the Maximum Tolerated Dose (MTD)/Maximum Administered Dose (MAD): additional sites may be added in order to ensure there is an acceptable enrolment rate; this is also dependent on tumour types of interest.

No of Patients:
The final sample size will depend on the number of Dose Limiting Toxicities (DLTs) observed at each dose level, any Cohort Review Committee (CRC) decision to assess an alternative treatment schedule, plus the enrichment cohort assessed at the MTD/MAD. However, no more than 30 evaluable patients would be considered feasible for the dose escalation portion of the study, and no more than 12 for the enrichment portion at the defined MAD/MTD.

Study Objectives and Endpoints:
The objectives of this study are to assess the safety, tolerability, pharmacokinetics (PK) and activity of VAL201 in patients with locally advanced or metastatic prostate cancer. Where a non-clinical rationale exists e.g. for fibrosarcoma or ovarian cancer, VAL201 may also be tested in a limited number of patients with other advanced solid tumours to confirm the MTD in these populations and assess preliminary anti-tumour activity.

Objective	Endpoint (Assessment)
Primary:	
• To estimate the MTD/MAD of VAL201	• DLT evaluation in 3-6 patients at the end of one treatment cycle
Secondary:	
• To assess the safety and tolerability of VAL201	• Ongoing evaluation of AEs during treatment and follow up
• To evaluate the pharmacokinetics of VAL201	• Assessment of pharmacokinetic variables (including, but not limited to, C_{max}, C_{min}, AUC)
• To assess anti-tumour activity of VAL201	• Response assessment by PCWG2 and/or other relevant response assessments e.g. RECIST 1.1
Exploratory:	
• To assess the pharmacodynamic (PD) activity of VAL201	• Assessment of biomarkers of VAL201 activity e.g. PhosphoERK kinase, WST-1, testosterone, oestrogen, PSA, and other relevant or exploratory biomarkers in blood, and in tumour biopsy material where possible
• To assess relevant tumour biomarkers	• Testing of archival and/or fresh tumour biopsy material where available

Study Design:
This is a Phase I/II, open-label, dose escalation study of the safety, tolerability, and PK of VAL201. The study will commence by enrolling patients with incurable, locally advanced or metastatic prostate cancer. Eligible participants will be enrolled in sequential cohorts treated with VAL201, given as a sub-cutaneous (s.c.) injection while being monitored for safety and DLTs.

The starting dose for the study will be 0.5 mg/kg VAL201 given on Days 1, 8 and 15 of a 3-week cycle, with a maximum feasible dose of 16 mg/kg. Dose increments will not exceed 100% and will be guided by safety data observed during Cycle 1, as well as continual assessment of safety beyond Cycle 1 in earlier cohorts, plus PK and PD data as available. Cohort 5 will introduce intra-patient dose escalation. with Cycle 1 Day 1 commencing at 8 mg/kg and escalating to 16 mg/kg at Cycle 4 Day 1. Escalation will be approved by the CRC on review of the safety and available PK and PD data. Each dose level will be evaluated for the occurrence of a DLT during the first cycle of treatment (Section 4.2.1).

Study cohorts: accelerated enrolment to 3+3 design
Due to calculated safety margins of the starting dose, the study will commence with an accelerated dose escalation schedule, with the first 2 cohorts enrolling 1 patient only (see Section 1.5). For each cohort, patients will be followed up for adverse events (AEs) and DLT during Cycle 1 and during the first cycle following each dose escalation. The CRC will review all patient safety data at the end of Cycle 1 and only permit dose escalation to the next dose level where there are no safety concerns. Where the CRC suspects that drug-related events have occurred that merit further exploration at that dose level, they will request that Cohort 1 or 2 must enrol 3 patients in order to more thoroughly

evaluate safety events prior to escalation. Cohorts of 3 patients will be enrolled from the 3rd cohort onwards (or earlier where the CRC recommend due to safety data evaluation). Dose escalation of 3-patient cohorts will proceed according to the scheme presented in Section 4.2.

Up to 6 cycles in total across all dose levels, are permitted within the main study. There will always be a stagger of at least 48 hours between dosing the first patient and subsequent patients at each dose. The CRC may request there be a further or prolonged stagger introduced depending on the nature of AEs observed to date.

Dose Limiting Toxicity

The CRC will agree on the next appropriate dose escalation step for each cohort primarily based on DLT evaluation during the first cycle at each new dose level. Only events occurring during the first cycle of treatment at each dose level will be considered for DLT determination; however, there will be on-going evaluation of AEs in subsequent treatment cycles which will be discussed during the cohort review process. Clinically significant events thought to be potentially related to VAL201, or trends in AEs seen in subsequent dosing cycles will be taken into account when considering future dose escalation steps and dose administration schedules. Upon occurrence of the first DLT within any cohort, additional patients will be added to that cohort so that up to a total of 6 can be evaluated. Once expansion to a 6-patient cohort has been recommended due to the identification of a DLT, escalation to the subsequent 3-patient cohort will only occur when all patients in the expanded cohort have completed their first cycle of VAL201 and no more than 1 DLT has occurred. If 2 or more DLTs occur in an expanded cohort, DLT is established at that dose level and the next lower dose level will be declared the MTD.

In Cohort 5, if a DLT occurs following dose-escalation (Cycles 4-6), patients recruited to expand the cohort will commence dosing from Cycle 1 at 8mg/kg and escalate as per protocol.

Note that intermediate dose levels may be explored below the dose level where 2 DLTs were seen in order to identify the maximum dose which may be safely administered. The protocol requires that 6 patients are dosed at the proposed MTD in order to confirm that the dose level is well tolerated. The highest dose where $\leq$ 1 DLT is seen in 6 patients will be termed the MTD. The CRC may also specify that a recruitment stagger be followed during cohort expansion for DLT evaluation depending on the nature of the DLT seen and the considered risk to patients.

The maximum single dose which may be administered is 16 mg/kg. Should this dose be reached without the need to de-escalate the dose due to DLT, it will be termed the MAD.

Safety evaluations will be conducted weekly during each treatment cycle, with DLT assessed during Cycle 1 only. All events and suspected DLTs will be graded according to the Common Terminology Criteria for AEs (CTCAE), version 4.03.

A DLT is defined as a VAL201-related Grade 3 or 4 AE that, in the opinion of the Investigator and/or CRC, represents a clinically significant hazard to the patient, with the following **exceptions** as considered appropriate by the CRC:

- 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 or less prior to the next administration);
- Symptomatic AEs, 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, reversibility, and in the context of the patient's medical history), and likely to be related to treatment with VAL201.

DLT events will also be considered in terms of inability to administer the planned Cycle 1 dose administration schedule. Clinically significant toxicity events considered related to VAL201 which lead to a dose delay of more than 7 days during Cycle 1, will be classified as DLTs (Section 4.2.1) Toxicity events must also be evaluated in terms of what is considered to be an appropriate next escalation step: in the case where the CRC agree that an escalation step of 33% or lower is merited, the toxicity of concern should be declared a DLT. The process for reporting suspected DLT events is described in the CRC Monitoring Plan.

Dose Escalation

In the absence of DLT or suggestion of VAL201-related events which would lead to more cautious dose escalation, the following dose escalation steps are recommended:

Cohort	No. of patients	Dose level
1	1*	0.5 mg/kg
2	1*	1.0 mg/kg
3	3	2.0 mg/kg
4	3	4.0 mg/kg
5	3	8.0 mg/kg escalating to a maximum of 16.0 mg/kg
6	3	Up to a maximum of 16.0mg/kg

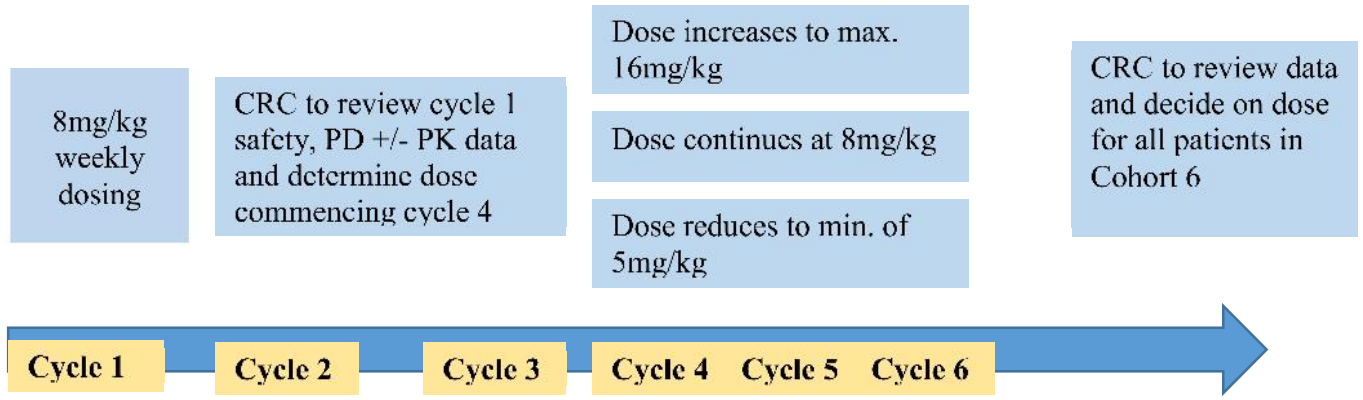
NB: all cohorts will be expanded to 6 patients upon identification of a DLT
*may be expanded to 3 to further investigate safety signal

The dose may be increased in sequential cohorts, up to a maximum of 16mg/kg, where the CRC consider it appropriate to do so, based on on-going evaluation of DLTs, AE and PK data.

In the case where a potentially significant toxicity occurs that is not a DLT, or a trend in toxicities is seen, considered to be related to treatment with VAL201, the CRC may decide to be more conservative in subsequent dose escalation and can agree to not exceed 50% of the previous dose. This restriction may be reversed where there is no suggestion of potentially clinical significant toxicity in the subsequent cohort(s). In the case where a single DLT event is observed, subsequent dose escalations will not exceed 33% of the previous dose.

All doses will be calculated based on the patient's weight at Screening, unless there has been more than 10% fluctuation in their body weight, whereby the new body weight will be used. Dose calculations will be capped at a maximum body weight of 100 kg for all patients weighing 100 kg or more.

Intra-patient dose escalation will be adopted in Cohort 5; the CRC will evaluate the safety and PK data following cycle 1 (dosed at 8mg/kg) and approve escalation to 16 mg/kg on Cycle 4 Day 1. Based on the review of the safety data, the CRC may suggest an alternative dose regimen for the patient if required, to a maximum of 16 mg/kg. If a DLT occurs at 8 mg/kg requiring dose de-escalation, subsequent doses may be reduced. If a DLT occurs at 16 mg/kg, subsequent doses may also be reduced, as an example to 12 mg/kg or lower as necessary. If the CRC have suggested an initial dose-escalation other than 16 mg/kg, they will suggest an appropriate dose reduction in the event of a DLT. Cohort 6 will enrol a further 3 patients at a dose of up to 16 mg/kg; the dose will be decided upon by the CRC guided by safety, PK and PD data available from Cohort 5.



Flow diagram to demonstrate Cycle 5 intra-patient dose escalation schedule and Cohort 6 dose selection.

Cohort Review Committee

All dose escalation decisions will be made by a CRC who shall convene to review all available AE, PK, PD and relevant patient data (see Section 8.1). The CRC will be composed of the trial investigators, sponsor, plus the study Medical Monitor. Additional experts may be invited to support the review of the data as required e.g. a pharmacokineticist. All data reviewed, CRC discussions and agreed dose escalation recommendations will be minuted. The composition and processes to be followed by the CRC will be described in the CRC Monitoring Plan which will be maintained in the TMF.

Based on evaluation of safety data from Cycle 1 of the current cohort, plus PK and PD data (where available), and on-going safety data from the trial, the CRC may also recommend dose de-escalation steps or adjustments in the dose administration schedule of VAL201. The CRC may also recommend that an alternative dose administration schedule of VAL201 be explored. Alternative dose schedules will be permitted as long as the total dose given in any **single dose** or over a **week or cycle** does not exceed the next dose level permitted following the study dose escalation rules.

Note that the MTD or MAD need not be confirmed for the original dose administration schedule prior to the CRC recommending the investigation of an alternative dose administration schedule. Multiple dose escalation tracks may be followed if more than one dose schedule is considered relevant to explore i.e. the CRC may recommend that the alternative dose administration schedule replaces a schedule or is explored in addition to another schedule.

Duration of treatment
The main study consists of up to 6 treatment cycles to be administered to each patient. Patients whose disease has not progressed and who have not been withdrawn from therapy due to toxicity will be eligible to continue receiving additional cycles of VAL201 beyond Cycle 6 where this is recommended by their Investigator. Such patients will continue to be followed up for toxicity and continued response (see Schedule of Study Assessments).

Enrichment at MTD or MAD

Once an MTD/MAD has been established for a given dose and schedule, up to an additional 12 patients with incurable, locally advanced or metastatic prostate cancer or other advanced solid tumours may be enrolled at this dose level (termed an "Enrichment Cohort") for further safety assessment and to obtain more data on preliminary anti-tumour activity at this dose level. During the MTD/MAD enrichment portion of the study, there will be on-going evaluation of safety data and further dose adjustments (dose schedule changes or de-escalations only) may be advised by the CRC during this period.

Cohort 6 will provide confirmation of safety in a further three patients, at the highest tolerated dose established.

Study Assessments:

The study will commence with a dosing schedule of VAL201 monotherapy given s.c. on Days 1, 8 and 15 of a 3-week cycle.

Patients will visit the study sites on each dosing day and/or every week at a minimum for a clinical examination and assessment of AEs. Laboratory screens will be assessed at each visit. Tumour assessment, with imaging (MRI, CT or bone scan where relevant), will be assessed in all patients at Screening and after every 3 cycles of treatment in Cohorts 5 and 6. Follow up assessments will be conducted in accordance with the Prostate Cancer Working Group 2 (PCWG2) reported consensus guidelines on the evaluation of prostate cancer patients in clinical trial (Scher, et al. 2008), RECIST 1.1 (Eisenhauer, et al. 2009) or other relevant response assessment guidelines as appropriate for the tumour type.

In Cohorts 1 to 4 a full PK profile was taken after the first and second doses of VAL201. Pre-dose samples were taken prior to doses on Cycle 1 Day 15, and Day 1 of Cycles 2 -6 during the dose escalation phase.

In Cohort 5 and 6, a full PK profile will be taken on Day 1 of cycles 1,3,4 and 6. Pre-dose samples and 1hr post-dose samples will be taken on Day 15 of cycles 1 and 4 and Day 1 of cycles 2 and 5.

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.

Inclusion/Exclusion Criteria:
The study will enrol patients with incurable, locally advanced or metastatic prostate cancer. The MTD/MAD may also be evaluated in patients with other advanced tumour types for whom no standard effective therapy is available and a rationale for use of VAL201 exists.

Inclusion Criteria
(i) Specific Inclusion Criteria for Patients with Prostate Cancer
1. Patients with incurable, locally advanced or metastatic prostate cancer who have relapsed following radiotherapy treatment, are in 'watchful waiting' or where a policy of intermittent hormone therapy has been decided. These patients must also have the following:
   a) rising PSA on three samples; each over 2 weeks apart, with the values being greater than 2 ng/mL higher than and at least 25% over the nadir.
   b) absent or very mild prostate cancer-related symptoms.
   c) no plans for any therapy for prostate cancer in the next two months.
2. Eastern Collaborative Oncology Group (ECOG) Performance Status (PS) of ≤ 1 (Appendix A).
3. Age ≥18 years at time of consent.

(ii) Specific Inclusion Criteria for Patients with Other Advanced Solid Tumours
4. Patients with histologically and/or cytologically confirmed advanced solid tumour for whom no standard effective therapy is available and a rationale for use of VAL201 exists e.g. fibrosarcoma, ovarian cancer.
5. Eastern Collaborative Oncology Group (ECOG) Performance Status (PS) of ≤ 2 (Appendix A).
6. Age ≥ 16 years at time of consent.

(iii) General Inclusion Criteria for all Patients
7. Evaluable disease, either measurable on imaging, or with informative tumour marker(s), as assessed by the PCWG2 or other relevant response assessment criteria for tumour type e.g. RECIST 1.1.
8. Recovery to baseline or CTCAE ≤ Grade 1, as determined by CTCAE v4.03 criteria (Appendix B), of reversible toxicities related to prior treatment, with the exception of alopecia, lymphopenia, other non-clinically significant AEs, including those considered related to androgen deprivation therapy.
9. Laboratory values at Screening:
   - Absolute neutrophil count ≥1.5 x 10^9/L;
   - Platelets ≥100 x 10^9/L;
   - Haemoglobin ≥90 g/L without blood transfusion or colony stimulating factor support;
   - Total bilirubin <1.5 times the upper limit of normal (ULN) (excluding patients with Gilberts Disease);
   - AST (SGOT) ≤2.5 times the ULN;
   - ALT (SGPT) ≤2.5 times the ULN; ≤5 x ULN for patients with advanced solid tumours with liver metastases;
   - Serum creatinine ≤1.5 x ULN or estimated glomerular filtration rate (GFR) of >50 mL/min based on the Cockcroft-Gault formula (see Appendix D).
10. 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 entry). 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 final administration of VAL201. Note that female patients may be surgically sterile (with appropriate documentation in the patient's medical records).

11. 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.
12. 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

(i) Specific Exclusion Criteria for Patients with Prostate Cancer

1. Patient has received an anti-cancer therapy, including investigational agents, within 6 weeks of Cycle 1, Day 1.
2. Patients who have undergone prior orchidectomy.

(ii) Specific Exclusion Criteria for Patients with Other Advanced Solid Tumours

3. Patient has received:
   a) any chemotherapy regimens (including investigational agents) with delayed toxicity within 4 weeks (6 weeks for prior nitrosourea or mitomycin C) of Cycle 1, Day 1, or received chemotherapy regimens given continuously or on a weekly basis which have limited potential for delayed toxicity within 2 weeks of Cycle 1, Day 1.
   b) radiotherapy, immunotherapy or biological agents (includes investigational agents) within 4 weeks of Cycle 1, Day 1. Localised palliative radiotherapy is permitted for symptom control.
4. Pregnant or lactating female patients.

(iii) General Exclusion Criteria for all Patients

5. Documented, symptomatic or uncontrolled brain metastases.
6. History of clinically significant cardiac condition, including ischemic cardiac event, myocardial infarction or unstable cardiac disease within 3 months of Cycle 1, Day 1.
7. Known human immunodeficiency virus positivity.
8. Active hepatitis B or C or other active liver disease (other than malignancy).
9. Any active, clinically significant, viral, bacterial, or systemic fungal infection within 4 weeks prior to Cycle 1, Day 1.
10. Any medical history that in the Investigator's opinion would jeopardize compliance with the protocol.

Route of Administration, Dose Schedule and Duration:

VAL201 is administered as a s.c. injection with a maximum total administration volume of 4.0 mL, and a maximum of 1.0 mL administered per injection site. In view of this, at higher doses it is permitted to administer VAL201 in multiple site injections (up to 4 sites). The starting dose level of VAL201 is 0.5 mg/kg given on Days 1, 8 and 15 of a 21-day cycle. The s.c. injection will be given following local administration guidelines including the use of premedication as required for local injection site reactions. The dose levels assessed in this study i.e. the dose and dosing administration schedules, may be adjusted following the study dose escalation rules, based on review of on-going evaluation of safety, PK and PD data generated during the study.

Statistical Methods:
There will be no formal statistical analysis in the dose-escalation phase this study. Results will be listed and summarised using descriptive statistics. An exact 95% CI will be calculated for the response rate observed in (i) Stage 1 (dose escalation) and (ii) Stage 2 (enrichment).

SCHEDULE OF STUDY ASSESSMENTS COHORTS 1-4

(i) For Day 1, 8 and 15 dosing schedule (main study)

	Screening	Cycle 1 (22 d cycle[10])					Cycle 2 – 5			Cycle 6			Final Cycle Visit/ C6 D22[11]	Final Study Visit[12]
	Day	Day					Day			Day				
	-28 to 0	1	2	8	9	15	1[10]	8	15	1[10]	8	15		
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	X	X
Vital signs[2]	X	X		X		X	X	X	X	X	X	X	X	X
ECG (resting 12-lead)[3]	X	X[3]					X[3]			X[3]			X[3]	X
Clinical chemistry*	X	X		X		X	X	X	X	X	X	X	X	X
Haematology	X	X		X		X	X	X	X	X	X	X	X	X
Coagulation	X	X		X		X	X	X	X	X	X	X	X	X
Urinalysis*	X	X					X			X				
Tumour assessment – prostate[4]	X	PSA only					X[4]			PSA only			(X[4])	(X[4])
Tumour assessment – other solid tumour[5]	X						X[5]						(X[5])	(X[5])
PD assessment – blood sample[6] (Up to 6 post dose samples)	X					X			X			X		
PD assessment – biopsy[7]	(X)	(X)												
Biomarker testing[8]	(X)													
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VAL201 administration		X		X		X	X	X	X	X	X	X		
Pharmacokinetics[9]		X	X	X	X	X	X			X				
Transfer to extended treatment													(X)[11]	

Footnotes - General

- Assessments made on Day 1 of each cycle are to be conducted prior to VAL201 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 and a tolerance of -1 day for all assessments relative to the study visit, unless specified otherwise.

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

SCHEDULE OF STUDY ASSESSMENTS - COHORT 5 and 6

(ii) For Day 1, 8 and 15 dosing schedule (main study)

	Screening	Cycle 1				Cycle 2			Cycle 3				Cycle 4				Cycle 5			Cycle 6				Final Cycle visit	Final study visit
	Day	Day				Day			Day				Day				Day			Day				C6D22	
	-28 to 0	1	2	8	15	1	8	15	1	2	8	15	1	2	8	15	1	8	15	1	2	8	15		
Informed consent	X																								
Demographics	X																								
Medical history	X																								
Inclusion/exclusion	X																								
ECOG PS	X					X			X				X				X			X				X	X
Physical examination[1]	X	X		X	X	X	X	X	X		X	X	X		X	X	X	X	X	X		X	X	X	X
Vital signs[2]	X	X		X	X	X	X	X	X		X	X	X		X	X	X	X	X	X		X	X	X	X
ECG (resting 12-lead)[3]	X	X[3]				X[3]			X[3]				X[3]				X[3]			X[3]				X[3]	X
Clinical chemistry*	X	X		X	X	X	X	X	X		X	X	X		X	X	X	X	X	X		X	X	X	X
Haematology	X	X		X	X	X	X	X	X		X	X	X		X	X	X	X	X	X		X	X	X	X
Coagulation	X	X		X	X	X	X	X	X		X	X	X		X	X	X	X	X	X		X	X	X	X
Urinalysis*	X	X				X			X				X				X			X					
Tumour assessment – prostate[4]	X[4]	X[4b]				X[4b]			X[4b]				X[4b]				X[4b]			X[4b]				(X[4d])	(X[4d])
Tumour assessment – other solid tumour[5]	X[5]												X[5]											(X)[5]	(X)[5]
PD assessment – blood sample[6] (Up to 6 post dose samples)	X				X			X				X				X			X				X		

	Screening	Cycle 1				Cycle 2			Cycle 3				Cycle 4				Cycle 5			Cycle 6				Final Cycle visit	Final study visit
	Day	Day				Day			Day				Day				Day			Day				C6D 22	
	-28 to 0	1	2	8	15	1	8	15	1	2	8	15	1	2	8	15	1	8	15	1	2	8	15		
PD assessment – biopsy[7]	(X)	(X)																							
Biomarker testing[8]	(X)	(X)																							
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VAL201 administration		X		X	X	X	X	X	X		X	X	X		X	X	X	X	X	X		X	X		
Pharmacokinetics[9]		X	X		X	X			X	X			X	X		X	X			X	X				
Transfer to extended treatment																								(X)[11]	

Footnotes - General

- Assessments made on Day 1 of each cycle are to be conducted prior to VAL201 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 and a tolerance of -1 day for all assessments relative to the study visit, unless specified otherwise.

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

Assessment Specific

1 **Cohorts 1-6:** Patient's height will be recorded at Screening. A full physical examination is required at Screening and prior to dosing 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 **Cohorts 1-4, 6:** Vital signs must be assessed at screening**.** On Cycle 1, Day 1 vital signs (heart rate, BP, temperature and respiration rate) will be assessed pre-dose and up to 1 hour after VAL201 administration. On all other dosing days, vital signs will be assessed pre-dose only. Patient status will be monitored during VAL201 administration and repeat vital signs will be taken if needed.
Cohort 5: On Cycle 1, Day 1 and Cycle 4, Day 1 vital signs (heart rate, BP, temperature and respiration rate) will be assessed pre-dose and up to 1 hour after VAL201 administration. On all other dosing days, vital signs will be assessed pre-dose only. Patient status will be monitored during VAL201 administration and repeat vital signs will be taken if needed.

3 **Cohorts 1-6:** Each assessment must be taken in triplicate. On Day 1 of each cycle a resting 12-lead ECG will be conducted pre-dose and 1 hour (+/- 15 min) after VAL201 administration. A single ECG is required only at screening and at the Final Study Visit.

4 Tumour assessment for prostate cancer patients will follow the PCWG2 guidelines and may include:
a) Cohorts 1-4:

- assessment of measurable disease in the chest and abdomen/pelvis (and selected non-measurable disease) by CT scan or MRI at Screening and after every 2 cycles of treatment (+/-1 week);
- assessment of serum PSA at Screening, C1D1 and every 3 weeks or at the end of every cycle;
- assessment of bone by whole body radionuclide bone scan at Screening and every 2-4 cycles of treatment as appropriate

b) **Cohort 5, 6:**

- assessment of measurable disease in the chest and abdomen/pelvis (and selected non-measurable disease) by MRI (or CT if MRI not possible) at Screening and after every **3 cycles of treatment** (+/-1 week);
- assessment of serum PSA at Screening C1D1 and **every 3 weeks or at the end of every cycle**;
- assessment of bone by whole body radionuclide bone scan at Screening and every **3 cycles** of treatment as appropriate

c) **Cohorts 1-6 :** Tumour assessment at the end of Cycle 6 is recommended to be performed at Cycle 6, Day 15 i.e. at -1 week, in order to assess suitability for extended treatment. Additional scans may be performed to confirm a Complete Response (CR) or Partial Response (PR) or disease progression (PD) as per PCWG2 guidelines. Other assessments e.g. whole body MRI may be assessed as requested by investigator.

d) Final Cycle Visit, Final Study Visit (Cohorts 1-6): Optional- PSA assessment (prostate cancer patients) and MRI (CT if not possible) +/-whole body radionuclide bone scan if not performed at the end of Cycle 6.

5 **Cohorts 1-6:** MRI (CT if not possible) performed at Screening and after every 3 cycles of treatment (+/- 1 week). Tumour assessment at the end of Cycle 6 is recommended to be performed at Cycle 6, Day 15 i.e. at -1 week, in order to assess suitability for extended treatment. Additional scans may be performed to confirm a Complete Response (CR) or Partial Response (PR) or disease progression (PD) as appropriate for tumour type and 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.

6 Assessment of PD activity will be conducted in all patients, and will require taking up to 7 blood samples for collection of plasma, PBMC and/or CTCs from Screening to Cycle 6. Time points for samples are from screening, and Day 15 of Cycles 1 – 6. For further detail, see Laboratory Procedures Manual.

7 Biopsies for PD evaluation are optional. Efforts will be made to collect a pre and post-dose biopsy sample from patients and imaging techniques may be used to facilitate this process. Post dose biopsy to be collected at Cycle 3 Day 15.

8 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, may be taken later during main study).

9 **Cohorts 1- 4 :** Patients enrolled to the dose escalation study will have PK sampling conducted at Cycle 1 at the following sample times. Two PK profiles may be taken: each will not exceed up to 13 samples (taken up to 24 hours post the end of administration; see example time points below). The CRC may advise on adjusted time-points. The maximum number of PK samples to be collected during any Cycle 1 dose schedule will not exceed 28. The actual time for each blood draw must be accurately recorded.

- Cycle1, Day 1: pre-dose (0h) then 5, 10, 15, 30 min, 1, 2, 3, 4, 6, 8, 10 and 24 h post-administration.
- Cycle 1, Day 8: pre-dose (0h) then 5, 10, 15, 30 min, 1, 2, 3, 4, 6, 8, 10 and 24 h post-administration.
- Cycle 1, Day 15 and Day 1 for all further cycles: immediately prior to administration

Cohort 5 - 6 : Patients enrolled to the dose escalation study will have PK sampling conducted at Cycle 1 at the following sample times. Two PK profiles may be taken: each will not exceed up to 11 samples (taken up to 24 hours post the end of administration; see example time points below). The CRC may advise on adjusted time-points. The maximum number of PK samples to be collected during any cycle will not exceed 13. The actual time for each blood draw must be accurately recorded

- Cycle 1 Day 1: pre-dose (0h) then 5, 10, 15, 30 min, 1, 2, 3, 5, 8, and 24 h post-administration
- Cycle 1 Day 15: pre-dose (0h) then 1h post-dose
- Cycle 2 Day 1: pre-dose (0h) then 1h post-dose
- Cycle 3 Day 1: pre-dose (0h) then 5, 10, 15, 30 min, 1, 2, 3, 5, 8, and 24 h post-administration
- Cycle 4 Day 1: pre-dose (0h) then 5, 10, 15, 30 min, 1, 2, 3, 5, 8, and 24 h post-administration
- Cycle 4 Day 15: pre-dose (0h) then 1h post-dose
- Cycle 5 Day 1: pre-dose (0h) then 1h post-dose
- Cycle 6 Day 1: pre-dose (0h) then 5, 10, 15, 30 min, 1, 2, 3, 5, 8, and 24 h post-administration

10 **Cohorts 1-6 :** Day 1 of Cycle 2-6 is Day 22 of Cycle 1-5, respectively.

11 **Cohorts 1-6 :** All patients will have Final Cycle Visit 1 week after their final dose in any cycle. Patients who complete treatment in Cycle 6 (i.e. they complete treatment to Cycle 6, Day 15), and who are not suitable for extended treatment with VAL201 will have their Cycle 6, Day 22 study assessments performed and continue to the Final Study Visit. Patients who complete treatment in Cycle 6 and who are considered suitable for extended treatment with VAL201 will have their Cycle 6, Day 22 assessments performed and must immediately be transferred to the extended treatment Schedule of Assessments in order to receive their Cycle 7, Day 1 dose (see Schedule of Assessments Tables iii).

12 **Cohorts 1-6 :** The Final Study Visit should be performed 30 +/-5 days after the last dose of VAL201 to enable a final safety assessment. Patients proceeding to receive extended treatment with VAL201 after completion of Cycle 6, will not have their Final Study Visit performed at this time.

(iii) Standard assessments for alternative dose schedules (main study Cohorts 1-6)

	Screening	Cycle 1				Cycle 2 –5			Cycle 6			Final Cycle Visit[12]	Final Study Visit[13]
	Day -28 to 0	Day 1	Day 2	Other dosing days	Interim assessment visit[10]	Day 1[11]	Other dosing days	Interim assessment visit[10]	Day 1[11]	Other dosing days	Interim assessment visit[10]		
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	X	X
Vital signs[2]	X	X		X	X	X	X	X	X	X	X	X	X
ECG (resting 12-lead)[3]	X	X[3]				X[3]			X[3]			X	X
Clinical chemistry*	X	X		X	X	X	X	X	X	X	X	X	X
Haematology	X	X		X	X	X	X	X	X	X	X	X	X
Coagulation	X	X		X	X	X	X	X	X	X	X	X	X
Urinalysis*	X	X				X			X				
Tumour assessment - prostate[4]	X	PSA only				X[4a,b]			PSA only		X[4b,c]	(X[4d])	(X[4d])
Tumour assessment - other solid tumour[5]	X	X									X[5]	(X[5])	(X[5])
PD assessment - blood sample[6]	X	X - up to 6 samples											
PD assessment - biopsy[7]	(X)	(X)											
Biomarker testing[8]	(X)												
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
VAL201 administration		X		X		X	X		X	X			
Pharmacokinetics[9]		X – max 28 samples to C2, D1				X			X				
Transfer to extended treatment												(X[12])	

Footnotes - General

- Assessments made on Day 1 of each cycle are to be conducted prior to VAL201 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 and a tolerance of -1 day for all assessments relative to the study visit, unless specified otherwise.

* ***safety bloods will include HBV & HCV 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 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, temperature and respiration rate) will be assessed pre-dose and up to 1 hour after VAL201 administration. On all other dosing days, vital signs will be assessed pre-dose only. Patient status will be monitored during VAL201 administration and repeat vital signs will be taken if needed.

3 Each assessment must be taken in triplicate. Day 1 of each cycle a resting 12-lead ECG will be conducted pre-dose and 1 hour (+/- 15 min) after VAL201 administration. A single ECG is required only at screening and at the Final Study Visit.

4 Tumour assessment for prostate cancer patients will follow the PCWG2 guidelines and may include:

a) Cohorts 1-4:

- assessment of measurable disease in the chest and abdomen/pelvis (and selected non-measurable disease) by CT scan or MRI at Screening and after every 2 cycles of treatment (+/-1 week);
- assessment of serum PSA at Screening, C1D1 and every 3 weeks or at the end of every cycle; and
- assessment of bone by whole body radionuclide bone scan at Screening and every 2-4 cycles of treatment as appropriate

b) Cohort 5, 6:

- assessment of measurable disease in the chest and abdomen/pelvis (and selected non-measurable disease) by MRI (or CT if MRI not possible) at Screening and after every **3 cycles of treatment** (+/-1 week);
- assessment of serum PSA at Screening and C1 D1 and **every 3 weeks or at the end of every cycle**;
- assessment of bone by whole body radionuclide bone scan at Screening and every **3 cycles** of treatment as appropriate

c) Cohorts 1-6 : Tumour assessment at the end of Cycle 6 is recommended to be performed at Cycle 6, Day 15 i.e. at -1 week, in order to assess suitability for extended treatment. Additional scans may be performed to confirm a Complete Response (CR) or Partial Response (PR) or disease progression (PD) as per PCWG2 guidelines. Other assessments e.g. whole body MRI may be assessed as requested by investigator.

d) Final Cycle Visit, Final Study Visit (Cohorts1-6): Optional- PSA assessment (prostate cancer patients) and MRI (CT if not possible) +/-whole body radionuclide bone scan if not performed at the end of Cycle 6.

5 CT or MRI performed at Screening and after every 2 cycles of treatment (+/- 1 week). Tumour assessment at the end of Cycle 6 is recommended to be performed at Cycle 6, Day 15 i.e. at -1 week, in order to assess suitability for extended treatment. Additional scans may be performed to confirm a Complete Response (CR) or Partial Response (PR) or disease progression (PD) as appropriate for tumour type and 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.

6 Assessment of PD activity will be conducted in all patients, and will require taking up to 7 blood samples for collection of plasma, PBMC and/or CTCs from Screening to Cycle 6.

7 Biopsies for PD evaluation are optional. Efforts will be made to collect a pre and post-dose biopsy sample from patients and imaging techniques may be used to facilitate this process.

8 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, may be taken later during main study).

9 Patients enrolled to the dose escalation study will have PK sampling conducted at Cycle 1 at the following sample times. Two PK profiles may be taken: each will not exceed up to 13 samples (taken up to 24 hours post the end of administration; see example time points below). The CRC may advise on an appropriate PK schedule and adjusted time-points. The maximum number of PK samples to be collected during any Cycle 1 dose schedule will not exceed 28. The actual time for each blood draw must be accurately recorded.

10 Interim assessment visits must be conducted at least weekly where there are no VAL201 dosing days within this time interval.

11 The first day of Cycle 2-6 is the same as the last day of Cycle 1-5.

12 All patients will have Final Cycle Visit 1 week after their final dose in any cycle. Patients who complete their treatment in Cycle 6 and who are not suitable for extended treatment with VAL201 will have their final study assessments performed for Cycle 6, then continue to the Final Study Visit. Patients who complete their treatment in Cycle 6 and who are considered suitable for extended treatment with VAL201 will have their final assessments performed for Cycle 6 and must immediately be transferred to the extended treatment Schedule of Assessments in order to receive their Cycle 7, Day 1 dose (see Schedule of Assessments Tables iii).

13 The Final Study Visit should be performed 30 +/-5 days after the last dose of VAL201 to enable a final safety assessment.

(iii) Day 1, 8 and 15 dosing schedule (extended treatment for all Cohorts)

	Cycle 7 onwards				Final Study Visit[8]
	Day				
	1[1,2]	8	15	22/1[7]	
ECOG PS				X	X
Physical examination[3]				X	X
Vital signs				X	X
ECG (resting 12-lead)[4]				X	X
Clinical chemistry				X	X
Haematology				X	X
Pregnancy test*	X			X	
Tumour assessment - prostate[5]				X	(X)
Tumour assessment - other solid tumour[6]				X	(X)
Adverse events		X	X	X	X
Concomitant medication		X	X	X	X
VAL201 administration	X	X	X	X	

Footnotes - General

- Assessments made on Day 1 of each cycle are to be conducted prior to VAL201 administration, unless specified otherwise.
- Additional assessments may be conducted as clinically indicated.
- A tolerance of +/-1 day will be permitted for all study visits and a tolerance of -1 day for all assessments relative to the study visit, unless specified otherwise.

* ***female patients require a urine pregnancy on Day 1 of each cycle***

Assessment Specific

1 Assessment for suitability for extended treatment will be made upon completion of treatment in Cycle 6 (see Schedule of Study Assessments Tables i and ii).

2 The final Cycle 6 study visit is the same as Cycle 7, Day 1. The Cycle 6, Day 22 visit assessments will be used for Cycle 7, Day 1.

3 Symptom-directed physical examination. Weight will be recorded at Day 1 of each cycle and at the Final Study Visit.

4 On Day 1 of each cycle a resting 12-lead ECG will be conducted pre-dose. Each assessment must be taken in triplicate. A single ECG is required at the Final Study Visit.

5 Tumour assessment for prostate cancer patients will follow the PCWG2 guidelines and may include:

- assessment of measurable disease in the chest and abdomen/pelvis (and selected non-measurable disease) by CT scan or MRI after every 4 cycles of treatment (+/-1 week);
- assessment of serum PSA per local practise e.g. every 3 weeks or at the end of every cycle; and
- assessment of bone by whole body radionuclide bone scan after every 4 cycles of treatment as appropriate.

Additional scans may be performed where clinically indicated or to confirm a Complete Response (CR) or Partial Response (PR) or disease progression (PD) as per PCWG2 guidelines. Other assessments e.g. whole body MRI may be assessed as requested by investigator.

6 CT or MRI performed at Screening and after every 4 cycles of treatment (+/- 1 week), or as clinically indicated. Additional scans may be performed to confirm a Complete Response (CR) or Partial Response (PR) or disease progression (PD) as appropriate for tumour type and 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.

7 Day 22 of each cycle is Day 1 of the next cycle. Patients may be withdrawn from VAL201 treatment at any time during a cycle. A Final Study Visit will be scheduled for 30 +/-5 days from their last dose of VAL201.

8 The Final Study Visit should be performed 30 +/-5 days after the last dose of VAL201 to enable a final safety assessment.

(iv) Standard assessments for alternative dose schedules (extended treatment)

	Cycle 7 onwards				Final Study Visit[9]
	Day 1[1,2]	Other dosing days	Interim assessments[7]	1[8]	
ECOG PS				X	X
Physical examination[3]				X	X
Vital signs				X	X
ECG (resting 12-lead)[4]				X	X
Clinical chemistry				X	X
Haematology				X	X
Pregnancy test*	X			X	
Tumour assessment - prostate[5]				X	(X)
Tumour assessment - other solid tumour[6]				X	(X)
Adverse events		X	X	X	X
Concomitant medication		X	X	X	X
VAL201 administration	X	X		X	

Footnotes - General

- Assessments made on Day 1 of each cycle are to be conducted prior to VAL201 administration, unless specified otherwise.
- Additional assessments may be conducted as clinically indicated.
- A tolerance of +/-1 day will be permitted for all study visits and a tolerance of -1 day for all assessments relative to the study visit, unless specified otherwise.

* ***female patients require a urine pregnancy on Day 1 of each cycle***

Assessment Specific

1 Assessment for suitability for extended treatment will be made upon completion of treatment in Cycle 6 (see Schedule of Study Assessments Tables i and ii).

2 The final Cycle 6 study visit is the same as Cycle 7, Day 1. The final Cycle 6 visit assessments will be used for Cycle 7, Day 1.

3 Symptom-directed physical examination. Weight will be recorded at Day 1 of each cycle and at the Final Study Visit.

4 On Day 1 of each cycle a resting 12-lead ECG will be conducted pre-dose. Each assessment must be taken in triplicate. A single ECG is required at the Final Study Visit.

5 Tumour assessment for prostate cancer patients will follow the PCWG2 guidelines and may include:

- assessment of measurable disease in the chest and abdomen/pelvis (and selected non-measurable disease) by CT scan or MRI after every 4 cycles of treatment (+/-1 week);
- assessment of serum PSA per local practise e.g. every 3 weeks or at the end of every cycle; and
- assessment of bone by whole body radionuclide bone scan after every 4 cycles of treatment as appropriate.

Additional scans may be performed where clinically indicated or to confirm a Complete Response (CR) or Partial Response (PR) or disease progression (PD) as per PCWG2 guidelines. Other assessments e.g. whole body MRI may be assessed as requested by investigator.

6 CT or MRI performed at Screening and after every 4 cycles of treatment (+/- 1 week), or as clinically indicated. Additional scans may be performed to confirm a Complete Response (CR) or Partial Response (PR) or disease progression (PD) as appropriate for tumour type and 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.

7 Interim assessments must be conducted at least weekly where there are no VAL201 dosing days within this time interval.

8 Day 1 of the next cycle.

9 The Final Study Visit should be performed 30 +/-5 days after the last dose of VAL201 to enable a final safety assessment.