STATISTICAL ANALYSIS PLAN

PROTOCOL: VAL201-001

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

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APPROVAL PAGE

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Lead Statistician details:	
Name:	[redacted]
Job Role:	
Company:	
Signature:	
Date of signature:	*YYY)*

Sponsor Approver details:	
Name:	[redacted]
Job Role:	
Company:	
Signature:	
Date of signature:	*YY)*

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Abbreviations

AE	Adverse Event
AUC	area under the plasma concentration versus time curve
AUC(0-t)	AUC from time zero to time t
$AUC_{0-\infty}$	the area under the concentration-time curve estimated from time zero to infinity as the sum of the two areas: AUC_{0-t} and AUC_{extrap}, where AUC_{extrap} is calculated as C_t / λ_z
CI	Confidence Interval
C_{inf}	the observed concentration at the end of the injection
CL	the systemic clearance calculated as: Dose/ $AUC_{0-\infty}$
C_{max}	maximum plasma concentration
C_{min}	minimum observed concentration
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CRC	Cohort Review Committee
DLT	dose limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ED50	50% of effective dose
ED90	90% of effective dose
h	hour
HBV	hepatitis B virus
HCV	hepatitis C virus
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Medicinal Products for Human Use
ITT	Intent to Treat
kg	Kilogram
L	Liter
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
ml	milliliter
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NA	Not Applicable
ng	nanogram
PD	pharmacodynamic(s) or progressive disease
PK	pharmacokinetic(s)

PSA	prostate-specific antigen
RECIST	Response Evaluation Criteria in Solid Tumours
s.c.	subcutaneous
SAE	serious adverse event
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emerged Adverse Event
t½	half-life
t_{max}	time to reach maximum concentration
Vss	the apparent volume of distribution at steady state calculated as: Dose/AUC x (AUMC/ AUC0-¥ - T/2) where T is the duration of intravenous injection
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

Revision History

Document Version	Changes Made	Document Date
Draft 1	Draft specification based on the following documents: • Study protocol VAL201-001 F2.0 • VAL201-001 CRF	24 AUG 2015
Draft 2	Updated draft after amendment	08 JUL 2016
Final	Updated after Sponsor comments	24 AUG 2016
Amendment Draft 1.0	Updates following protocol amendment VAL201-001 version F5.0	29 JAN 2018
Amendment Draft 2.0	Updates following protocol amendment VAL201-001 version F6.0	17 JUN 2019
Amendment Final 2.0	Finalized Amendment version after Sponsor confirmation	05 SEP 2019
Amendment Draft 2.1	Updates following early study termination decision	10 FEB 2020
Amendment Draft 2.2	Updates following discussion with Sponsor	11 JUN 2020
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1. Introduction

The present Statistical Analysis Plan (SAP) outlines analysis to guide the programming for the data analyses of clinical study VAL201-001 protocol version F6.0 (last version - 7.0 - of study protocol was finalized and approved but never implemented for use in the study). The study was closed to further recruitment in January 2020 due to difficultly in recruiting patients to meet the inclusion/ exclusion criteria within the current protocol; the treatment paradigm for patients had significantly evolved during the five years of patient recruitment being open. Any changes to the study protocol or Case Report Form (CRF) may necessitate updates to the SAP. In case of deviations from the finalized SAP, explanations will be provided in the clinical study report.
Relevant applicable CROS NT Standard Operating Procedures (SOP) will be followed in compliance with the agreement with the Client.

2. Study Objectives

The objectives of this clinical study are to assess the safety, tolerability, pharmacokinetics (PK) and activity of VAL201 in patients with incurable, locally advanced or metastatic prostate cancer. VAL201 may also be tested in patients with other advanced solid tumours. The inclusion of limited number of patients with other advanced solid tumours will confirm the MTD and assess preliminary anti-tumour activity.

2.1.1 Primary objective

The primary objective of this clinical study is to estimate the Maximum Tolerated Dose (MTD)/Maximum Administered Dose (MAD) of VAL201 in cancer patients with advanced solid tumors.
MTD refers to a dose with an acceptable and manageable safety profile, in the absence of the MTD MAD refers to the highest dose level administered.

2.1.2 Secondary objectives

The secondary objectives of this clinical study are:
- To assess the safety and tolerability of VAL201.
- To evaluate the pharmacokinetics of VAL201.
- To assess anti-tumour activity of VAL201.

2.1.3 Exploratory objectives

This clinical study includes two exploratory objectives:
- To assess the pharmacodynamic (PD) activity of VAL201.
- To assess relevant tumour biomarkers.

3. Study Design

3.1 General design and plan

This clinical study is designed to establish the MTD/MAD, safety, tolerability and PK of VAL201 by testing the drug (VAL201) on patients with incurable, locally advanced or metastatic prostate cancer and other advanced solid tumors. The design is a Phase I/II, open-label single-arm dose escalation study. The study design consists of a dose escalation part followed by an enrichment part. The study features includes: five cohorts of up to six patients, six cycles (main study) each cycle will last 21 days and an extended treatment period of VAL201 if a patient is considered suitable. Events that occur during each cycle will be considered for Dose Limiting Toxicity (DLT) assessment and therefore to establish the MTD/MAD.

The dose escalation will follow an accelerated enrolment of 3+3 design where the first two cohorts will enroll 1 patient each with an accelerated dose escalation schedule as described on Section 4.2 of the clinical study protocol (VAL201-001 version F6.0). Each patient will be followed up for AEs and DLT during each cycle. Where the Cohort Review Committee (CRC) suspects that drug-related events have occurred that merit further exploration at that dose level, they will request that the cohort 1 or 2 must enroll 3 more patients in order to 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). After a DLT has been identified the cohort will be expanded to 6 patients. If a second DLT is reported this will be declared the MTD.

The starting dose of VAL201 for the first cohort of patients will be 0.5 mg/kg/dose given on Days 1, 8 and 15 of each cycle. In the absence of DLT, the dose of VAL201 will be escalated for future cohorts in recommended increments according to the rules for dose escalation as described in Section 4.2 of clinical study protocol. All dose escalation decisions will be made by a CRC who shall convene to review all available safety data.

Intra-patient dose escalation will be adopted in Cohort 5; the CRC will evaluate the safety, clinical observations 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.

Cohort 6 will enroll 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.

Once the MTD/MAD has been established for a given dose and schedule, up to 12 additional patients with incurable, locally advance prostate cancer or other advance solid tumours may be enrolled at this dose level (termed as “Enrichment Cohort”).

Thirty evaluable patients will be enrolled for the dose escalation part of the study and no more of 12 patients for the enrichment part of the study at the defined MTD/MAD for a total of 42 patients.

3.2 Visit Schedule and Visit Windows

The study design for the starting dose of VAL201 includes the following visit schedule and visit windows:

Window	Description	Visit window	
		Min (day)	Max (day)
Screening	Within 28 days of enrollment to Cycle 1 Day 1	-28	0
Cycle 1	Visits scheduled at Day 1, Day 2, Day 8, Day 9, Day 15	1	1
Cycle 2 - 5	Visits scheduled at Day 1 (Day 22 of the previous Cycle), Day 8, Day 15	1	1
Cycle 6	Visits scheduled at Day 1 (Day 22 of Cycle 5), Day 8, Day 15	1	1
Final Cycle Visit	This visit is performed one week after the final dose of VAL201 in any cycle	1	1
Final Study Visit	This visit is performed 30 days after the final dose of VAL201 in any cycle	5	5

Where the CRC recommend an adjustment to the dose schedule, the following visit schedule and visit windows will be performed:

Window	Description	Visit window	
		Min (day)	Max (day)
Screening	Within 28 days of enrollment to Cycle 1 Day 1		
Cycle 1	Visits scheduled at Day 1, Day 2, Day 8, Day 15	1	1
Cycle 2 - 5	Visits scheduled at Day 1 (Day 22 of the previous Cycle), Day 8, Day 15	1	1
Cycle 6	Visits scheduled at Day 1 (Day 22 of Cycle 5), Day 8, Day 15	1	1
Final Cycle Visit	This visit is performed one week after the final dose of VAL201 in any cycle	1	1
Final Study Visit	This visit is performed 30 days after the final dose of VAL201 in any cycle	5	5

Where a patient continues to receive VAL201 after completion of main study, the following visit schedule and visit windows will be performed:

Window	Description	Visit window	
		Min (day)	Max (day)
Cycle 7 onwards	Visits scheduled at Day 1 (Day 22 of Cycle 6), Day 8, Day 15	1	1
Final Study Visit	This visit is performed 30 days after the final dose of VAL201 in any cycle	5	5

The activities that will be performed at each cycle and day are summarized in the protocol under SCHEDULE OF STUDY ASSESSMENTS (table i, table ii and table iii).

3.3 Sample size justification

Up to 42 patients with incurable, locally advanced or metastatic prostate cancer or other advanced solid tumours may be enrolled in this study. It will follow a dose escalation design, and the number of patients treated will therefore be dependent upon the number of dose levels investigated.
A conventional algorithm (3+3 patients per dose level) will be used to identify the MTD or MAD, escalating on 0/3 or 1/6 DLTs, and de-escalating if 2 or more patients with DLTs are encountered. The MTD will be the highest dose level at which 0 of 3 or 1 of 6 patients experience a DLT, with the next higher dose having at least 2 of 3 or 2 of 6 patients experiencing a DLT.

The following table shows the operating characteristics of this 3+3 design. Under this design, there is a 71% chance of escalation if the true but unknown rate of DLT is 20% and less than 50% chance of escalation if the true but unknown rate of DLT is higher than 30%.

Operating characteristics of the 3+3 study design

True but Unknown Rate of DLT (%)	Probability of Escalation (%)
20	71
30	49
40	31
50	17
60	8

3.4 Assessment of the objectives

In the dose escalation phase, an exact 95% CI will be calculated for the response rate observed. No further formal statistical analysis will be performed. In the enrichment phase of the study the following assessment were planned to be performed:

3.4.1 Secondary objective assessment

- Evaluation of AEs during treatment and follow up.
- Assessment of pharmacokinetics measures.
- Tumor assessments following PCWG2 and RECIST 1.1 recommendations and may include the following as appropriate:
    - assessment of measurable and any selected non-measurable lesions by MRI scan (or CT if not possible) of chest, and abdomen/pelvis at Screening and

  on the completion of every 2 cycles (every 3 cycles in Cohorts 5 and 6);

- assessment of PSA levels in serum at screening and every 3 weeks (or at the end of each cycle);
- assessment of bone lesions by a whole-body radionuclide scan at Screening and on the completion of every 2-4 cycles (3 cycles in Cohorts 5 and 6);
- other assessments e.g. whole body MRI may be assessed as requested by investigator.

- percent change in PSA from baseline to tumour assessment time point;
  Percent change = [1 – exp(ln(PSAcx/PSAb))]*100;

  where:
  PSAb is the PSA at the screening (day -28 to 0)
  PSAcx is the PSA at day 1 of each cycle (x indicates the cycle 1 to 7 and onwards)
- maximum decline in PSA during study defined as the maximum reduction in PSA from the baseline (looking at all visits, following Cycle 1 Day 1, which is indeed Baseline Visit for PSA, up to the last final cycle visit or the last dosing visit, if final cycle visit is not present, inclusive); this value will be determined by the percent change in PSA from baseline, a negative percent will indicate a decline in PSA.
- based on the three pre-treatment PSA values, an estimate of pre-treatment PSA doubling time will be derived by regressing the natural log of the PSA values versus the time points, the slope of the regression will be used to estimate pre-treatment PSA doubling time
  $Ln(PSA) = a + bt_x$
  doubling time: ln(2)/b
  where ln is the natural logarithm
  a is the intercept,
  b is the slope,
  t_x are the time where the PSA test was performed.

3.4.2 Exploratory objective assessment

- Assessment of pharmacodynamics activity of VAL201.
- Assessment of tumour biomarkers.

3.5 Safety endpoints

The safety analysis will include all patients screened and enrolled for whom has been given at least one dose by subcutaneous (s.c.) injection of VAL201.
The number and percent of subjects experiencing Adverse Events (AEs) will be reported by dose. In addition the incidence of AE and suspected DLTs will be graded according to the Common Terminology Criteria for AEs (CTCAE), version 4.03.

In order to assess the primary objective of the analysis the following classification of the safety variables will be apply:

Dose Limiting Toxicity (DLT)

A DLT is defined as a drug –related Grade 3 or 4 AE (from CTCAE version 4.03) that, in the opinion of the Investigator and/or CRC, represents a clinically significant hazard to the patient; a list of exceptions is presented in Section 4.2.1 of the study protocol.

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.

Pre-treatment adverse events-

An AE will be classified as pre-treatment AE if it starts before the date/time of day of first medication intake in the study.

Treatment-emergent adverse event (TEAE)

An AE will be classified as a TEAE if it starts on or after the date/time of day 1 cycle 1 of the study. In case of missing or incomplete dates/times not allowing a direct allocation to any of the two categories of AEs, it will be considered to be treatment-emergent, unless the stop date is known to be prior to the first administration of the study medication. The AE will be allocated to the first category allowed by the available data, according to the following order:

- TEAE
- Pre-treatment.

Serious adverse event (SAE)

A SAE is an AE judged as serious.

Adverse Event Related to study drug

An AE is considered as related to study drug if it is judged as “Possibly Related”, “Probably Related” or “Definitely Related” or with missing relationship.

Adverse event leading to death

Every adverse event (AE) including serious adverse event (SAE) is recorded and graded for severity according to the CTCAE v4.03. An adverse event (AE), including a serious adverse event (SAE), with a severity outcome equal to “Death related to AE” (Grade 5 from CTCAE version 4.03) is by definition an adverse event leading to death.

Count of adverse events

Two AEs with the same Preferred Term (PT) and classified in the same category (pre-treatment AE or TEAE) will be considered as two different events when calculating the “number of events” in the tables, unless they have same onset time and date.

4. Statistical Analysis

4.1 General

Results for dose-escalation phase will be listed and summarized using descriptive statistics. An exact 95% CI will be calculated for the response rate observed in dose escalation phase.
Descriptive summaries of continuous variables in terms of observed values will be provided. These summaries will contain arithmetic mean, SD, minimum, median and maximum or geometric mean and %CV in place of the arithmetic mean and SD for data requiring log transform due to known skewness (e.g. PSA).
Descriptive summaries of categorical variables will consist of frequencies and percentages.
All statistical analysis (i.e.: both efficacy and safety) will be done according to the actual treatment received due to the protocol's flexibility in allowing the cohort review committee to adjust the dose of individual patients. The most frequent dose taken by a subject during all treatment occasions in each cycle will be used for subject assignment to each treatment (dose) group for the purpose of the analysis; this is to cover any dosing subjects may have received by mistake occasionally only.

Any unscheduled visits will not be used for summary tables, but listed only.

4.2 Analysis sets

The statistical analyses will be based on analysis sets defined in the following sections.

4.2.1 Intent to Treat set

All subjects that received at least one dose of VAL201 will be included. Patients enrolled for the dose escalation part of the study will be replaced if they withdraw for reasons other than a DLT associated event.

4.2.2 Per Protocol set

The per-protocol (PP) set, a subset of the ITT, will include all subjects that complete the main study (cycles 1 to 6). Subjects that do not complete the main study and subjects with major protocol deviations that may affect the data will be excluded from the PP set.
The classification of major and minor protocol deviations and the resulting definition of analysis sets will be performed prior to the analysis and will be approved by the Sponsor. The determination of protocol deviations and their assessment will be fixed in the evaluability plan.
A summary of the number of subjects per analysis set will be given and reasons for exclusion of a subject from an analysis set will be listed in the evaluability listing.

4.2.3 Safety set

The safety set will include all patients that have been given at least one dose by subcutaneous (s.c.) injection of VAL201.

4.2.4 PK set

The PK set will include all subjects in the safety set with evaluable PK data (i.e.: all patients with a calculated concentration available).

4.3 Sub-group analyses

NA.

4.4 Handling of missing and incomplete data

Missing values will be included in the denominator count when computing percentages. Only the non-missing values will be evaluated for computing summary statistics. 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 VAL201.
In order to calculate the duration of tumor, the following rules will be applied for partial dates of histological/cytological diagnosis:

- if only the day is missing, the 15th of the month will be assumed;
- if the day and the month are missing, 30th June will be assumed.

4.5 Derived Variables

Age
Subject age (in years) will be captured on the CRF at the Screening (day -28 to 0).

Body Mass Index (BMI) (kg/m^2)
BMI will be calculated at Screening using the following formula:

$$\text{BMI} = \frac{\text{Body weight}\,(\text{kg})}{(\text{height}\,(\text{cm})/100)^2}$$

Duration of tumour (years)

Duration of tumour will be calculated using the following formula:

Duration of tumour = (Informed Consent signature date - Date of histological/cytological diagnosis +1)/365.25

Responder subject (for response rate calculation) – prostate cancer subjects only
A subject is defined responder if completed 6 treatment cycles without being labelled as having disease progression by PCWG2 criteria in any cycle, i.e. if all the 4 PCWG2 Evaluation questions, included in the TUMOR ASSESSMENT – PROSTATE/ PCWG2 EVALUATION CRF Form, are answered as “No” this indicate no progression for the subject.

4.6 Changes in the planned analysis

The SAP has been updated due to changes in the study design (see Protocol Amendment Version 5 and 6). The main changes are:

- Cohort 5 will start treatment on a dose of 8mg/kg (rather than 5mg/kg). Moreover, from cycle 4 day 1 onwards, the dose may change.
- The schedule for the following parameters has changed: vital signs, tumor assessment, and pharmacokinetics.
- For each cohort, patients will be followed up for DLT not only during the first cycle, but during each cycle.

Furthermore, due to the premature closure of the study, the analysis on enrichment phase will not be produced. This phase was not reached within the study.
Any assessments available on Final cycle 6 day 22/cycle 7 day1, will be included in the planned summary tables by cycle produced on the main study phase.
The following exploratory endpoints will also not analyzed, as per Sponsor decision:

- Assessment of additional pharmacodynamics activity of VAL201. PD assessment is limited to only those parameters contained within Clinical Chemistry (Testosterone, LH, PSA).
- Assessment of tumour biomarkers.

4.7 Software

All analyses will be conducted using SAS® version 9.2 or later.

5. Evaluation of Demographic and Baseline Characteristics

5.1 Subject enrolment and disposition

A screened subject is a subject who has completed the activities at the Screening Visit (-28 to 0 days before day 1 cycle 1), met the inclusion and exclusion criteria, and signed the Informed Consent Form. Summary of the number of subjects in the ITT, PP and Safety sets will be provided for the dose escalation part of the study. The number and percentage of subjects who withdrew from the study and the reasons for early study termination will be summarized for the dose escalation part of the.

5.2 Protocol violations

The classification of major and minor protocol deviations and the resulting definition of analysis sets will be performed at the end of the study by the clinical study team and assessed as “minor” or “major” in consultation with the Sponsor. Major protocol deviations are defined as those deviations from the protocol likely to have an impact on the perceived safety and tolerability of study treatments.

A summary of all randomized subjects with at least one minor or major protocol deviation will be summarized in number and percentage by type of deviation and treatment group. A by-subject listing of major protocol deviations will also be provided.

5.3 Study discontinuations

As it is stated on section 3.4 of study protocol: if a patient is withdrawn from the study for reasons other than a DLT-associated event before the end of cycle 1 during the dose escalation portion of the study, the patient will be replaced; whereas patients who withdraw from the study or discontinue treatment after completion of cycle 1 will not be replaced.
The number of subject withdrawals and the number of subjects completing the study will be summarized. This summary will include the reasons for discontinuation.

5.4 Demographics and baseline characteristics

The subjects enrolled in the study will be statistically characterized for baseline, demographic and clinical characteristics using descriptive statistics (mean, median, standard deviation, etc.) for continuous factors such as, but not limited to, age body mass index (BMI), and by frequency and percentage distributions for categorical factors such as, but not limited to gender, race.
All summaries of continuous characteristics will be based on non-missing observations; in addition the number of missing observation will be shown. For categorical characteristics, percentages will be calculated out of the total number of subjects in the data set (i.e., each denominator includes the number of subjects with missing/unknown values for the characteristic such as but not limited to race, gender, ECOG PS etc.).
Baseline characteristic include:

- Medical history
- Concomitant medication
- ECOG Performance Status
- Full physical examination (including height and weight)
- Vital signs
- ECG (resting 12-lead)
- Clinical Chemistry (include HBV & HCV testing at Screening)
- Haematology
- Coagulation
- Urinalysis
- Tumour assessment prostate

5.5 Medical and surgical history

Medical history

A disease is considered as medical history if it is not ongoing at screening visit ("ongoing" box is not ticked).

Concomitant disease
A disease is considered as concomitant disease if it is ongoing at screening visit ("ongoing" box is ticked).

Medical history and/or concomitant diseases will be summarised by system organ class (SOC) and preferred term (PT) using the MedDRA system (version 17.0).
Study cancer history information, as collected in the related CRF form, will be listed only.

5.6 Prior and concomitant medications

The medication documented on the concomitant medication page will be analyzed as follows:

- Prior medication, if the last intake was prior to day of first medication intake,
- Concomitant medication, if the intake was between day of first medication intake and study termination.

If the day or month of the start date is unknown, the medication will be analyzed using the available information. If this information is not sufficient for the division into one of the above mentioned categories, the worst case will be used (e.g. start date = NK/05/2015, end date = 13/05/2015, date of termination = 12/05/2015 → concomitant medication).
The analysis will be performed using the preferred name (WHO Drug Dictionary 2015). The levels used will be "Anatomical Therapeutical Chemical Classification" (ATC) and "Medication product Name" (MP).
Study cancer therapies as collected in the dedicated CRF form will be listed only.

5.7 ECOG Performance Status

Eastern Co-operative Oncology Group (ECOG) Performance Status is performed at the screening and at day 1 of cycle 2 to cycle 6 before administration of the test drug. Descriptive statistics of the ECOG PS grade will be provided by screening and by cycle (cycle 2 – 6).

5.8 Physical Examination

Full physical examination (including height and weight) will be performed at screening and at day 1, day 8 and day 15 of each cycle. Clinically significant abnormalities in physical examination will be recorded as adverse event (AE). Physical examination will be listed by phase (dose escalation phase), by cycle and time point. In addition, height and weight will also be listed.

5.9 Vital Signs

Vital signs (Systolic Blood Pressure [SBP], Diastolic Blood Pressure [DBP], Heart Rate [HR], Respiratory Rate [RR] and body temperature) will be assessed at screening, and depending on the cohorts, as follows:

- For cohorts 1, 2, 3, 4 and 6 vital signs will be assessed at day 1 cycle 1 before the administration of the test drug and up to 1 hour after the administration of the test drug and at dosing days of each cycle (day 1, day 8, day 15) before administration of the test drug;
- For cohort 5 vital signs will be assessed at day 1 cycle 1 and at day 1 cycle 4 before the administration of the test drug and up to 1 hour after the administration of the test drug and at dosing days of each cycle (day 1, day 8, day 15) before administration of the test drug;

In case of multiple assessments done in the same visit/time point, the average of the values will be calculated and used for the analysis. All assessments will be included in subject data listings.

Listings will be provided and summary of the data will be tabulated by cycle.

5.10 ECG (resting 12-lead)

The electrocardiogram (resting 12-lead) will be assessed in triplicate at the screening, at day 1 of each cycle before administration of the test drug and 1 hour (+/- 15 mins) after administration of the test drug. A listing of the following parameter will be presented for each patient: 12-lead electrocardiogram (ECG) parameters: Heart rate, PR interval, QRS duration, QTc interval, QTcF interval.

5.11 Clinical Chemistry (include HBV & HCV testing at Screening), Haematology, Coagulation and Urinalysis

Laboratory parameters will be assessed at screening, day 1, day 8 and day 15 of each cycle; except for the Urinalysis which will be assessed at screening and day 1 of each cycle. Data will be listed for dose escalation phase by dose group where applicable and cycle. In addition, descriptive statistics, with respect to the investigator's interpretation (Normal, NCS = Abnormal Not Clinically Significant, CS = Abnormal Clinically Significant, NR = No Result), will be presented by cycle and time point.
In case of multiple assessments done in the same visit/time point, the latest one (looking at date and time recorded) will be used for the analysis; in case of missing assessment time, preference will be given to assessments on same date but with time information available. All assessments will be included in subject data listings.

5.12 Tumour assessment prostate

Tumour assessment for prostate cancer patients will follow the PCWG2 guidelines or RECIST 1.1 guidelines and may include assessment of serum prostate-specific antigen (PSA) at screening and every 3 weeks or at the end of every cycle.

A summary table for tumour assessment at screening and at each applicable cycle will be produced presenting descriptive statistics for longest tumour diameter (mm) reported as well as duration of tumour (years) and method of examination; longest tumour diameter will be classified by tumour location and such categories will be defined by a study medical expert reviewing the related information collected.
The assessment of prostate-specific antigen PSA outcomes will be summarised for each patient and time point including the percent change in PSA from baseline to tumour assessment time point.
An estimate of pre-treatment PSA doubling time will be presented in a summary table together with descriptive statistics for PSA values at each cycle and the related percent change from baseline.
Baseline PSA value is defined as the last available assessment before treatment start (which will be actually the PSA value collected at Cycle 1 Day 1).
Thereafter tumour assessment and prostate-specific antigen PSA assessment results will be listed, including also maximum decline in PSA during study.
If other methods were used to assess the tumour such CT scan or MRI then the results of the tests will be listed for each patient by time point.

6. Evaluation of objectives

The evaluation of the primary objective will be based on the safety set, the evaluation of the secondary objective will be based on the ITT set and the evaluation of the exploratory objective will be based on the ITT set and the PP set separately. Tables and listings will be presented separately.

6.1 Analysis of primary objective

The primary objective of this study is to estimate the MTD/MAD of VAL201 throughout an accelerated dose escalation design (3+3 patients per dose level). The first 2 cohorts will enroll 1 patient only (see Section 1.5 of the study protocol). For each cohort, patients will be followed up for adverse events (AEs) and DLT during each cycle.
The escalating dose will be determined if 0 patients out of 3 or 1 patient out of 6 experience a DLT, and de-escalating if 2 or more patients with DLTs are encountered. Therefore the MTD will be the highest dose level at which 0 of 3 or 1 of 6 patients experience a DLT.
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 enroll 3 more 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) thereafter the cohort will be expanded to 6 patients upon identification of a DLT. If a second DLT is reported this will be declared the MTD.
There will be no formal statistical analysis in the dose-escalation phase. However, safety data such as AEs and DLT will be listed and summarised by dose level separately using descriptive statistics. Pre-treatment AEs will be listed.

6.2 Analysis of secondary objectives

The secondary objectives of this study are: safety, tolerability, pharmacokinetics (PK) and anti-tumour activity of VAL201.

6.2.1 Assessment of the safety and tolerability

The assessment of safety and tolerability will be based on the safety data set; the evaluation of AEs will be carried throughout every cycle including follow up period, which is defined as final study visit performed 30 +/- 5 days after last dose of VAL201.
Frequencies and percentages of patients experiencing one or more AEs will be summarized and listed by:

- Dose level where applicable.
- Relationship to the study drug.
- Severity.

Severe Adverse Events (SAEs) and DLTs will be presented separately.
The number of AEs leading to death and treatment emergent AE (TEAE) will be summarised by descriptive statistics. Aes will be coded using the MedDRA dictionary (version 17.0). The SOCs and PTs will be used for tabulation. The number and the percentage of patients with at least one AE will be presented by SOC and PT.

Safety parameters such as vital signs will be listed and summarized as described in section 5.10 of this SAP. Laboratory parameters such as haematology, coagulation, clinical chemistry and urinalysis data will be listed and summarised as indicated in section 5.11 of this SAP. Physical examination and ECG parameters will be listed as indicated in section 5.8 and 5.10 respectively of this SAP.

6.2.2 Evaluation of the pharmacokinetics parameters

The following PK parameters will be derived for each subject from the individual plasma concentration versus time profiles of VAL201: Tmax, Cmax, t(1/2) AUC(0-t), AUC (0-inf), AUMC (0-t), lambda, Cl/F, Vz/F.

All PK variables (except for T_{max}) will be listed.
Patient profile treatment concentrations will be produced (one figure with each individual patient included in the PK population).
A plot of the mean profile of treatment concentration (One figure with means Concentration-Time Curve on a Linear Scale with SD) will also be produced.

6.2.3 Evaluation of anti-tumour activity of VAL201

For patients with prostate cancer or other tumour types where applicable, response rate (assessed by PCWG2 for prostate cancer or RECIST 1.1 for other tumour types), was planned to include CT (or MRI), radionuclide bone scan, and PSA at the selected dose level and assessed in a 2 stage analysis

(dose escalation and enrichment respectively). Stage 2 was not reached within the study and only prostate cancer patients were finally included in the trial, so response rate will be summarized for Dose Escalation Stage only, based on responder definition reported in section 4.5; exact 95% CI will be calculated. Prostate Specific Antigen assessment will be summarized as indicated in section 5.12 of this SAP.

6.3 Analysis of exploratory objectives

The planned exploratory objectives of this study were: pharmacodynamics (PD) activity of VAL201 and assessment of tumour biomarkers. Due to the early termination of the study, the related exploratory endpoints will not be analyzed. PSA, LH and Testosterone only, will be included as part of the descriptive analysis for laboratory biochemistry (see section 6.2.1).

7. Tables, Figures and Listings

7.1 Tables

Tables will be provided for the display of data from this study and are numbered following the ICH E3 “Structure and Content of Clinical Study Report”.
All tables will be presented in landscape format.
The standard font size is 9 points Courier New for all tables.

Titles will be center-aligned; footnotes will be left-aligned.
Each table will have 2 titles:

- The 1st title will be the table/figure number with the description of the table;
- The 2nd title will be a description of the study population presented in the table.

Some tables will have a third title (before 2nd title) with a description of the statistical method used in those tables.

Any footnote added to explain the table contents will be presented in the following format:
Note 1: Percentages are calculated on the number of patients (N).
Note 2: A serious adverse event is an ....
Note 3: …….

The last two footnotes of each table will be footers indicating:

- the reference listing of the data;
- the program name, the date and time of generation and the SAS® version used.

7.2 Tables listings and figures

7.2.1 Tables:

TABLE 14.1-1	DISPOSITION OF PATIENTS / SUMMARY OF ALL PATIENTS AND ANALYSIS SET
TABLE 14.1-2.1	SUMMARY OF MAJOR PROTOCOL DEVIATION / INTENT TO TREAT POPULATION
TABLE 14.1-2.2	SUMMARY OF MINOR PROTOCOL DEVIATION / INTENT TO TREAT POPULATION
TABLE 14.1-3.1	DEMOGRAPHIC CHARACTERISTIC / INTENT TO TREAT POPULATION
TABLE 14.1-4	SUMMARY OF TUMOUR ASSESSMENT / INTENT TO TREAT POPULATION
TABLE 14.1-5.1	MEDICAL HISTORY BY SYSTEM ORGAN CLASS AND PREFERRED TERM / INTENT TO TREAT POPULATION
TABLE 14.1-5.2	CONCOMITANT DISEASE BY SYSTEM ORGAN CLASS AND PREFERRED TERM / INTENT TO TREAT POPULATION
TABLE 14.1-6.1	PREVIOUS MEDICATIONS / INTENT TO TREAT POPULATION
TABLE 14.1-6.2	CONCOMITANT MEDICATIONS / INTENT TO TREAT POPULATION
TABLE 14.2-1	SUMMARY OF DOSE LIMITING TOXICITY (DLT) BY COHORT / SAFETY POPULATION
TABLE 14.2-3.1	PROSTATE SPECIFIC ANTIGEN (PSA) ASSESSMENT / INTENT TO TREAT POPULATION
TABLE 14.2-3.2	PROSTATE SPECIFIC ANTIGEN (PSA) ASSESSMENT / PER PROTOCOL POPULATION
TABLE T14.2-4.1	SUMMARY OF RESPONSE RATE ANTI TUMOUR ACTIVITY / INENT TO TREAT POPULATION
TABLE T14.2-4.2	SUMMARY OF RESPONSE RATE ANTI TUMOUR ACTIVITY / PER PROTOCOL POPULATION
TABLE T14.3.1-1.1	SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS BY DOSE/ DOSE ESCALATION SAFETY POPULATION
TABLE T14.3.1-2.1	SUMMARY OF TREATMENT EMERGENT ADVERSE EVENT BY SYSTEM ORGAN CLASS AND BY DOSE / DOSE ESCALATION SAFETY POPULATION
TABLE T14.3.1-3.1	SUMMARY OF TREATMENT EMERGENT ADVERSE EVENT BY SYSTEM ORGAN CLASS AND BY SEVERITY / DOSE ESCALATION SAFETY POPULATION
TABLE T14.3.1-4.1	SUMMARY OF TREATMENT EMERGENT ADVERSE EVENT BY SYSTEM ORGAN CLASS AND BY CAUSALITY / DOSE ESCALATION SAFETY POPULATION
TABLE 14.3.4-1.1	ESTERN CO-OPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS / INTENT TO TREAT POPULATION
TABLE 14.3.4-1.2	ESTERN CO-OPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS / PER PROTOCOL POPULATION
TABLE 14.3.4-2.1	SUMMARY VITAL SIGNS BY CYCLE AND VISIT / INTENT TO TREAT POPULATION

TABLE 14.3.4-2.2	SUMMARY VITAL SIGNS BY CYCLE AND VISIT / PER PROTOCOL POPULATION
TABLE 14.3.4-3.1.1	LABORATORY PARAMETERS: CLINICAL CHEMISTRY BY CYCLE AND TIME POINTS / INTENT TO TREAT POPULATION
TABLE 14.3.4-3.1.2	LABORATORY PARAMETERS: HAEMATOLOGY AND COAGULATION BY CYCLE AND TIME POINTS / INTENT TO TREAT POPULATION
TABLE 14.3.4-3.1.3	LABORATORY PARAMETERS: URINALYSIS BY CYCLE AND TIME POINTS / INTENT TO TREAT POPULATION
TABLE 14.3.4-3.2.1	LABORATORY PARAMETERS: CLINICAL CHEMISTRY BY CYCLE AND TIME POINTS / PER PROTOCOL POPULATION
TABLE 14.3.4-3.2.2	LABORATORY PARAMETERS: HAEMATOLOGY AND COAGULATION BY CYCLE AND TIME POINTS / PER PROTOCOL POPULATION
TABLE 14.3.4-3.2.3	LABORATORY PARAMETERS: URINALYSIS BY CYCLE AND TIME POINTS / PER PROTOCOL POPULATION

7.2.2 Listings:

LISTING 16.2.1-1	DISPOSITION OF PATIENTS / ALL PATIENTS
LISTING 16.2.2-1	PROTOCOL DEVIATIONS / INTENT TO TREAT POPULATION
LISTING 16.2.3-1	DEMOGRAPHIC AND BASELINE CHARACTERISTICS / INTENT TO TREAT POPULATION
LISTING 16.2.4-1	PHYSICAL EXAMINATIONS / INTENT TO TREAT POPULATION
LISTING 16.2.4-2	PAST-CONCOMITANT DISEASES / INTENT TO TREAT POPULATION
LISTING 16.2.4-3	STUDY CANCER HISTORY / INTENT TO TREAT POPULATION
LISTING 16.2.4-4	TUMOUR ASSESSMENT / INTENT TO TREAT POPULATION
LISTING 16.2.5-1	MEDICATIONS / INTENT TO TREAT POPULATION
LISTING 16.2.6-1	PROSTATE SPECIFIC ANTIGEN (PSA) / INTENT TO TREAT POPULATION
LISTING 16.2.6-2	OTHER SOLID TUMOUR / INTENT TO TREAT POPULATION
LISTING 16.2.7-1	PRE-TREATMENT ADVERSE EVENTS / INTENT TO TREAT POPULATION
LISTING 16.2.7-2.1	TREATMENT-EMERGENT ADVERSE EVENTS / SAFETY POPULATION
LISTING 16.2.7-2.2	SERIOUS TREATMENT-EMERGENT ADVERSE EVENTS / SAFETY POPULATION
LISTING 16.2.7-2.3	TREATMENT-EMERGENT ADVERSE DRUG REACTIONS / SAFETY POPULATION
LISTING 16.2.7-2.4	TREATMENT-EMERGENT ADVERSE EVENTS LEADING TO DISCONTINUATION / SAFETY POPULATION
LISTING 16.2.7-2.5	TREATMENT-EMERGENT ADVERSE EVENTS AS CODED / SAFETY POPULATION

LISTING 16.2.8-1	VITAL SIGNS / INTENT TO TREAT POPULATION
LISTING 16.2.8-2	12-LEAD ECG / INTENT TO TREAT POPULATION
LISTING 16.2.8-3	ESTERN CO-OPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS / INTENT TO TREAT POPULATION
LISTING 16.2.8-4.1	LABORATORY PARAMETERS: CLINICAL CHEMISTRY / INTENT TO TREAT POPULATION
LISTING 16.2.8-4.2	LABORATORY PARAMETERS: HEAMATOLOGY AND COAGULATION / INTENT TO TREAT POPULATION
LISTING 16.2.8-4.3	LABORATORY PARAMETERS: URINALYSIS / INTENT TO TREAT POPULATION
LISTING 16.2.8-6	PK PARAMETERS / PK POPULATION

7.2.3 Figures:

FIGURE F14.2-1.1	PATIENT PROFILE OF TREATMENTS CONCENTRATIONS / PK POPULATION
FIGURE F14.2-1.2	MEAN PROFILE OF TREATMENTS CONCENTRATIONS / PK POPULATION

8. Appendices

See document “Val201-001_SAP_Appendix_Amendment _3.0.docx”.