CLINICAL STUDY PROTOCOL – AMENDMENT ~~11~~12

APPLIES TO ALL INVOLVED COUNTRIES

SAFETY AND PHARMACOKINETICS OF ODM-208 IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Study code:	3124001
Study design:	Open-label, non-randomised, uncontrolled, multicentre, dose escalation, first-in-human study with a dose expansion
Short study title:	CYPIDES
Phase:	I/II
Standard:	GCP
EudraCT number:	2017-002534-23
Study Coordinating Investigator:	Karim Fizazi
Sponsor:	Orion Corporation ~~Orion Pharma~~ Orionintie 1, FI-02200 Espoo, Finland
Date:	25 October 2022~~7 June 2021~~

Sponsor approvals:

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SYNOPSIS

Sponsor: Orion Corporation Orion Pharma
Finished product: Not applicable
Active pharmaceutical ingredient: ODM-208
Study title: Safety and pharmacokinetics of ODM-208 in patients with metastatic castration-resistant prostate cancer
Study code: 3124001
Investigator: The study coordinating investigator is Prof. Karim Fizazi
Study centres: This will be a multinational study. It is planned that 3-5 sites will participate in Part 1/Phase 1 of the study, with an approximately 15 additional sites in Part 2/Phase 2 of the study.
Development phase: I/II
Objectives: **Part 1/Phase 1:** Primary objectives are: • to evaluate the safety and tolerability of ODM-208 in patients with metastatic castration-resistant prostate cancer (mCRPC), • to define the maximum tolerated dose (MTD) and dose limiting toxicities (DLTs) of ODM-208, if possible, • to define the recommended dose of ODM-208 for Part 2 of the study. Secondary objectives are: • to characterise the pharmacokinetics (PK) of ODM-208 after single and repeated administration, • to evaluate dosing schedule of ODM-208, • to evaluate preliminary antitumour activity of ODM-208. **Part 2/Phase 2:** Primary objectives are: • to further evaluate the safety and tolerability of ODM-208, • to further evaluate the preliminary antitumour activity of ODM-208 in mCRPC patients with and without mutated androgen receptor (AR) ligand-binding domain (LBD) who have progressed after novel AR targeted therapy and taxane-based chemotherapy. Secondary objectives are: • to evaluate different AR LBD mutations and their association with antitumour activity of ODM-208.
Methodology: This is an open-label, non-randomised, uncontrolled, multicentre, dose escalation, first-in-human study containing a dose escalation part (Part 1A Group 1 and Part 1A Group 2), an optional part for further evaluation of dosing (Part 1B) and a cohort expansion part (Part 2). **Part 1/Phase 1** of the study consists of a screening period of maximum 21 days, a treatment period for each patient lasting as long as it is considered beneficial to the patient (as judged by the investigator), or until death, intolerable toxicity or any other discontinuation criterion is met, and a post-treatment period (28 days). If needed, adrenal recovery will be followed after the end-of-study visit (EOS) (for a maximum of 24 weeks). In addition, the study consists of an optional pre-screening period for a mutation analysis of the androgen receptor gene. A 3+3 rule-based design will be used in the dose escalation component (Part 1A). The dose escalation will be based on the review of PK, pharmacodynamic (PD) and safety data by the Safety Monitoring Board (SMB) and the maximum allowed incremental increase can be 100% in absence of toxicity. Further evaluations on the dosing or the dosing conditions of ODM-208 can be done in the Part 1B. Part 1 dose levels, as well as the dose for Part 2, will be recommended by the SMB. **Part 2/Phase 2** of the study consists of a pre-screening period for centralized analysis of the AR LBD mutations in plasma circulating tumour DNA (ctDNA), and a screening period of maximum 21 days. The treatment period will continue until disease progression (after disease progression the treatment may be continued if the patient is considered to clinically benefit from the treatment as judged by the investigator), or until death, intolerable toxicity or any other discontinuation criterion is met. The study contains a post-treatment period (28 days), and if needed, adrenal recovery will be followed after the end-of-study visit (for a maximum of 24 weeks). Survival status will be recorded at long-term follow-ups.

Number of patients: It is expected that maximum 72 patients will be enrolled in Part 1/Phase 1 and approximately 640 AR LBD mutation positive patients ~~in Part 2/Phase 2~~ and approximately 60 AR LBD mutation negative mCRPC patients in Part 2 (added in Amendment 12).
Diagnosis and main criteria for inclusion: Male subjects aged ≥ 18 years with progressive mCRPC can be enrolled into this study. Patients must maintain ongoing androgen deprivation therapy with a gonadotropin-releasing hormone (GnRH) analogue, antagonist, or have had bilateral orchiectomy. Patients must have received at least one prior line of novel hormonal AR targeted therapy and at least 1 line of taxane-based chemotherapy in castration-sensitive prostate cancer (CSPC) or in CRPC, and must have life expectancy over 3 months and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. For Part 2/Phase 2 only: equal numbers of patients ~~must have~~will be enrolled with and without ~~identified~~ an activating mutation in the LBD of AR in plasma ctDNA confirmed by the central testing.
Investigational medicinal product, dose and mode of administration: ODM-208 is provided in 1 mg, 5 mg, 25 mg, and 50 mg tablets for oral administration. **Part 1/Phase 1:** Starting daily dose of ODM-208 for patients in Cohort 1 of Part 1 dose escalation is 100 mg (50 mg twice daily) with food. The highest achieved individual ODM-208 exposure with corticosteroid replacement therapy in 28-day toxicology study in dog (AUC_{0-24} 36 500 h*ng/ml) is considered the initial maximum exposure level of ODM-208 in human, which should not be exceeded in phase 1 dose escalation. **Part 2/Phase 2:** Dose of ODM-208 is 5 mg twice daily with food (Added in Amendment 7).
Auxiliary medicinal products, dose and mode of administration: **Part 1/Phase 1:** Dexamethasone 0.5 mg and 1 mg, prednisone/prednisolone 5 mg tablet, hydrocortisone 10 mg tablet, and fludrocortisone 50 µg tablet for oral administration. Dexamethasone will be administered once a day, prednisone/prednisolone twice a day, hydrocortisone 3 times a day and fludrocortisone once a day. **Part 2/Phase 2:** Dexamethasone 0.5 mg and 1 mg and fludrocortisone 50 µg or 100 µg tablets will be used. Dexamethasone 1.5 mg and fludrocortisone 100 µg ~~dose will be~~are recommended starting doses administered once a day, the doses can be adjusted, if clinically indicated.
Frequency/duration of treatment: Patients can continue to receive ODM-208 treatment until disease progression (after disease progression the treatment may be continued if it is considered clinically beneficial to the patient, as judged by the investigator), or until death, intolerable toxicity or any other discontinuation criterion is met, whichever occurs first.
Bioanalytical method: Concentrations of ODM-208 will be determined using a validated liquid-chromatography-tandem mass spectrometry (LC/MS/MS) method.
Variables and methods of assessments **Assessment of antitumour effects:** PSA: Serum total prostate specific antigen (PSA) concentrations will be determined. PSA response or progression will be evaluated using the Prostate Cancer Working Group 3 (PCWG3) criteria. Soft tissue response: Chest, abdomen and pelvic computed tomography (CT) or magnetic resonance imaging (MRI) will be performed. Changes in tumour burden will be assessed using the Response Evaluation Criteria In Solid Tumours (RECIST) 1.1. Objective response rate (ORR) i.e. the rate of complete (CR) and/or partial responses (PR) by RECIST 1.1 will be assessed. Bone: Radionucleotide bone scans will be performed. The status of bone metastases will be assessed using the PCWG3 criteria. ECOG performance status: ECOG performance status will be assessed. Time to ECOG performance deterioration will be assessed. Clinical disease progression: Assessment of the disease progression during the study will be based on PSA, imaging and clinical status, and it is characterised by e.g. a decrease in patient's ECOG score, clinically significant loss of appetite, weight loss (more than 10% from baseline), or increase in pain. The decision regarding disease progression is made by the investigator based on available data. Time to PSA progression will be assessed according to the PCWG3. Time to radiographic progression will be assessed by either RECIST progression and/or progression on bone scan by PCWG3. Duration of objective response will be assessed.

Radiographic progression-free survival (rPFS) by either RECIST progression and/or progression on bone scan by PCWG3.

Time on treatment will be assessed.

Part 2/Phase 2 only: Circulating tumour cell (CTC) response rate will be assessed and defined as the proportion of patients with CTC count nonzero at baseline and 0 at 12 weeks (CTC0). Overall survival will also be assessed.

Assessment of PK variables:

Part 1/Phase 1: Blood samples will be collected for determination of the concentrations of ODM-208 in plasma and for determination of plasma protein binding of ODM-208. ODM-208 metabolites will be screened from blood and urine. The PK parameters (C_{max}, t_{max}, AUC_t, AUC_∞, λ_z, V_z/F, Cl/F and $t_{½}$) will be calculated from the concentration-time data of ODM-208 after single dose administration on Day 1 and after repeated dosing on Day 8. Additionally C_{av} will be calculated as $AUC_{0\text{-}12h}$ divided by the dosing interval (12 h) for twice daily dosing after repeated dosing on Day 8. Pre-dose concentrations (C0) of ODM-208 on Day 29 and Week 12 will be reported.

Part 2/Phase 2: Blood samples will be collected for determination of ODM-208 in plasma. ODM-208 concentration relationship to PD, PSA and safety will be evaluated.

Assessment of PD variables and other biomarkers:

PD variables: Testosterone and other steroid assessments will be performed to study PD effects of ODM-208. Other steroids that may be assessed if analytically feasible are e.g. androstenedione, dehydroepiandrosterone sulfate (DHEA-S), pregnenolone, 11-ketotestosterone (11KT), and 11βhydroxyandrostenedione (11OHA4).

Explorative biomarkers: Blood will be collected for exploratory plasma assessments. In Part 2/ Phase 2 blood will be collected for evaluation of AR splice variant AR-V7 status in CTCs.

Germline DNA and pharmacogenomics (PG): Blood will be collected for possible germline DNA and PG assessments.

Assessment of safety:

Safety will be assessed by the evaluation of adverse events (AEs), laboratory tests, physical examination findings, heart rate (HR), systolic and diastolic blood pressure (BP), orthostatic test (Part 1 only), 12-lead electrocardiograms (ECGs).

Statistical methods:

Data will be tabulated with descriptive statistics pooled by part and mutation status as appropriate.

Analysis of efficacy – antitumour effects

PSA: PSA data will be analysed descriptively by dose and study part. The number of responders (30% and 50% decline from baseline) at 12 weeks will be presented. Also number of patients with decrease in PSA from baseline will be tabulated by time point and by best response.

Soft tissue response: The frequency of responders according to RECIST 1.1 criteria of soft (target and non-target) lesions will be presented. Descriptive statistics of sum of lesion diameters and percent changes will be presented. ORR will be tabulated with descriptive statistics. ORR will be presented as best response and by time point.

Bone: Bone progression (PCWG3) and the changes from baseline in the number of lesions on bone scan will be reported as “no new lesions” or “new lesions”.

CTC response will be tabulated with descriptive statistics.

ECOG performance status and time to ECOG deterioration: The ECOG performance status changes from baseline will be reported with descriptive statistics. Time to ECOG deterioration will be summarised by Kaplan-Meier method.

Clinical disease progression: Clinical disease progression symptoms will be summarised.

Time to disease progression: Median time to both PSA progression (deaths censored) and radiographic progression with RECIST 1.1 and PCWG3 criteria (deaths censored) will be summarised with descriptive statistics and Kaplan-Meier method.

Duration of objective response will be summarised with descriptive statistics.

rPFS will be summarised with descriptive statistics and Kaplan-Meier method.

Time on treatment: The time from the start of ODM-208 treatment until discontinuation of ODM-208 treatment will be summarised with descriptive statistics and Kaplan-Meier method, if appropriate.

Overall survival will be summarised with descriptive statistics and the Kaplan-Meier method.

Pharmacokinetic analysis

Part 1/Phase 1: The PK variables (C_{max}, t_{max}, AUC_t, AUC_∞, V_z/F, Cl/F and $t_{½}$) will be summarised separately after single and repeated dosing using descriptive statistics, and plotted with appropriate figures. The dose proportionality of ODM-208 on the PK variables AUC_t and C_{max} will be analysed using a general linear regression model ('power model') for the log-transformed AUC_t and C_{max} values. The comparison of PK results of ODM-208 between single dose and repeated dose administration will be made by a linear mixed model, including sampling day as repeated factor, and dose level as a between factor.

Part 2/Phase 2: PK will be summarized using descriptive statistics. A population PK and PK/PD model for ODM-208 is planned to be developed. Population PK and PK/PD modelling may be applied to evaluate the role of covariates and PK/PD relations in terms of safety and efficacy related variables.

Pharmacodynamic and biomarker analyses:

Steroid variables: The actual values and the changes from baseline for testosterone and other steroid variables will be summarised using descriptive statistics.

Explorative plasma biomarker assessments will be summarised by descriptive statistics and may be reported as separate reports, as appropriate.

AR mutation data will be tabulated using descriptive statistics.

PG: Genetic polymorphisms may be analysed in relation to significant variation or specific scientific question in PK, PD or safety variables of ODM-208. If such descriptive analysis are performed, the results will be reported in separate report.

Safety analysis

The safety population will include all patients who have taken at least 1 dose of study medication. Adverse events (AEs) will be classified by system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) coding system. The AEs will be graded by toxicity grade classified by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. AEs, vital signs, orthostatic test (Part 1 only), physical examinations, ECGs and laboratory safety data will be summarised using descriptive statistics.

ABBREVIATIONS AND DEFINITION OF TERMS

ACTH	Adrenocorticotropic hormone
ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine aminotransferase
AMP	Auxiliary medicinal products
AR	Androgen receptor
AST	Aspartate aminotransferase
AUC_t	Area under the concentration-time curve from time zero to the last sample with a quantifiable concentration
AUC_∞	Area under the concentration-time curve from time zero to infinity
BP	Blood pressure
CA	Competent authority
C_{av}	Average concentration in plasma
CBG	Corticosteroid-binding globulin
CI	Confidence intervals
Cl/F	Apparent clearance following oral administration.
C_{max}	Maximum concentration in plasma
CNS	Central nervous system
CR	Complete response
CRF/eCRF	Case report form/electronic case report form
CRO	Contract research organisation
CRPC	Castration-resistant prostate cancer
CSPC	Castration-sensitive prostate cancer
CT	Computed tomography
CTC	Circulating tumour cell
ctDNA	Circulating tumour DNA
CYP	Cytochrome P450
DHT	Dihydrotestosterone

DHEA-S	Dehydroepiandrosterone sulfate
DLT	Dose limiting toxicity
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EOS	End-of-study
ePRO	Electronic patient-reported outcome
FT4	Free thyroxine
GCP	Good clinical practice
G-CSF	Granulocyte colony stimulating factor
GI	Gastrointestinal
GLP	Good laboratory practice
GMP	Good manufacturing practice
GnRH	Gonadotropin-releasing hormone
GR	Glucocorticoid receptor
HBA1c	Glycated haemoglobin
HDL	High-density lipoprotein
HED	Human equivalent dose
hERG	Human Ether-à-go-go-Related Gene
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HR	Heart rate
IC	Informed consent
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intention-to-treat
i.v.	Intravenous

LBD	Ligand binding domain
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LDL	Low-density lipoprotein
LLOQ	Lower limit of quantification
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No-observed-adverse-effect level
ORR	Objective response rate
OS	Overall survival
PCWG3	Prostate Cancer Working Group 3
PBPK	Physiologically based pharmacokinetic
PD	Pharmacodynamic(s)
PFS	Progression-free survival
PG	Pharmacogenomic(s)
PK	Pharmacokinetic(s)
PP	Per-protocol
PR	Partial response
PSA	Prostate specific antigen
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious adverse event
SMB	Safety monitoring board
STD 10	Severely toxic dose in the 10 % of animals
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Terminal elimination half-life
TC	Telephone contact

TSH	Thyroid-stimulating hormone
t_{max}	Time to reach maximum concentration in plasma
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution during elimination phase
λ_z	Terminal elimination rate constant
11OHA4	11β-hydroxyandrostenedione
11KT	11-ketotestosterone
11KDHT	11-ketodihydrotestosterone

Note on usage of terms:

Orion Corporation ~~Orion Pharma~~ is hereafter in this document called “Orion”.

The term ‘investigator’ in the text of the protocol refers to the principal investigator or co-investigator.

1. INTRODUCTION

1.1 Background

1.1.1 Overview of disease epidemiology and current treatment

Advanced prostate cancer is a major cause of cancer morbidity and mortality worldwide (Ferlay J et al., 2013). Although prostate cancer is initially sensitive to androgen deprivation therapy (ADT), progression despite castrate levels of testosterone eventually occurs, and patients enter the lethal form of the disease, known as castration-resistant prostate cancer (CRPC). Many treatment options are currently available for CRPC ranging from androgen receptor (AR) targeting agents abiraterone acetate and enzalutamide, docetaxel and cabazitaxel, radiopharmaceutical radium-223, to vaccine sipuleucel-T. Despite treatment options, the challenge for managing CRPC is the limited duration of clinical and survival benefits by offered treatments due to primary and acquired resistance. The median overall survival for patients upon developing CRPC is in the range of 14-24 months (Halabi S et al., 2014).

Reactivation of AR signalling axis plays a critical role in CRPC. The growth mechanisms of CRPC tumours in the castrate environment are incompletely understood. It has been hypothesised that increased intratumoral androgen synthesis, AR gene amplification or overexpression, and AR mutations that increase affinity for low potency androgens may result in tumour growth in the castrate environment. It has also been shown that expression of steroidogenic gene transcripts is changed in CRPC, indicating altered steroid synthesis profile to produce androgens (Stanbrough M et al., 2006, Mitsiades N et al., 2012).

The clinical relevance of targeting androgen signalling in metastatic CRPC (mCRPC) is demonstrated by the survival advantage conferred by the newer AR-targeted agents abiraterone acetate (CYP17A1 inhibitor) in combination with prednisone and enzalutamide (AR antagonist). In abiraterone treated patients, up-regulation of CYP17A1, alternative ligand synthesis and AR splice variants are suggested as mechanisms for driving disease progression. The potent CYP17A1 inhibition leads to accumulation of upstream androgens, which may use alternate steroid synthesis pathway that ultimately leads to dihydrotestosterone (DHT) (Attard G et al., 2012). Recently also significant increases in the level of progesterone were reported in patients treated with abiraterone (Bertaglia V et al., 2017). Interestingly, the increased progesterone levels have been suggested to be one of the resistance mechanisms especially via mutated AR (Mostaghel EA et al., 2011, Sharifi N, 2015). It has also been suggested that long-term use of prednisone could lead a selection of AR mutations that are activated by prednisone leading to disease progression. In a retrospective small study in patients with CRPC (N=30), who have progressed on treatment with abiraterone and prednisone, a steroid switch to dexamethasone resulted in a ≥ 30% decline in prostate specific antigen (PSA) levels in 39.2% of patients and a median time to PSA progression of 11.7 weeks (Lorente D et al., 2014). However, as no mutational analyses were performed, a role of prednisone in disease progression remains speculative. Point mutations in the AR gene have been reported to occur at a comparatively high incidence in patients with mCRPC, especially in tumours progressing under the second-generation AR signaling inhibitors. Mutations in the AR may have various effects, including loss of function, increased or decreased AR signalling. Most of these mutations are located in the ligand-binding domain (LBD) of AR and appear to be somatic events. Gain-of-function mutations in the LBD of AR result in nonspecific activation of AR by weak androgens, progestins, glucocorticoids, estrogens and antiandrogens. One of the most frequently observed

mutations is the T878A mutation which appears to arise in patients taking abiraterone together with prednisone (Boudadi K et al., 2016). The H875Y mutation in the AR LBD is associated with acquired resistance to e.g. abiraterone with prednisone and enzalutamide (Romanel A et al., 2015, Jernberg E et al., 2017). One of the AR LBD mutations, which confers activation of AR by glucocorticoids is L702H. This mutation has been reported in patients treated with abiraterone together with prednisone or dexamethasone. AR LBD mutation F877L is frequently reported mutation in patients treated with enzalutamide and apalutamide. This mutation it is known to confer resistance to the treatments (Boudadi K et al., 2016). AR splice variants and glucocorticoid receptor (GR) induction are suggested to be other resistance mechanisms in enzalutamide treated patients (Isikbay M et al., 2014, Antonarakis ES, 2015).

Recently it has been published that the adrenal steroid 11β-hydroxyandrostenedione (11OHA4) can serve as a precursor to 11-ketotestosterone (11KT) and 11-ketodihydrotestosterone (11KDHT), which were shown to be potent and efficacious agonists of AR (Pretorius E et al., 2016). 11KT and 11KDHT steroids have been measured in plasma and prostate cancer tissue from patients, suggesting a potential role as activate androgens in CRPC (du Toit T et al., 2017).

The optimal sequence of agents for treatment of mCRPC is unclear and no clear guidelines exist on optimal treatment sequences. Data on use of abiraterone after disease progression on enzalutamide and taxanes (Loriot Y et al., 2013) and use of enzalutamide after disease progression on abiraterone and taxanes (Brasso K et al., 2015) suggest significantly lower antitumour activity compared to the phase III trials with abiraterone (COU-301-AA) and enzalutamide (AFFIRM). Small retrospective studies have demonstrated modest PSA response rates (≥50% in 7-8%), and short durations of progression-free survival (PFS) (2.6-3.4 months) on abiraterone in patients after progressing with enzalutamide (Loriot Y et al., 2013, Yamada Y et al., 2016). The median overall survival and PSA responses (≥ 50% in 18%) were also modest on enzalutamide treatment in patients following disease progression on taxane-based chemotherapy and abiraterone (Brasso K et al., 2015).

ODM-208 is a novel nonsteroidal selective inhibitor of CYP11A1 (cytochrome P450 cholesterol side-chain cleavage enzyme, P450scc), blocking enzymatic activity of the first step of the steroidogenic pathway in which cholesterol is converted to pregnenolone. This inhibition leads to deficiency to produce androgens, glucocorticoids and mineralocorticoids.

~~1.1.1~~1.1.2 Non-clinical and in vitro data

In vitro, ODM-208 inhibited CYP11A1 with a half maximal inhibitory concentration (IC_{50}) value of 104 nM. Further, formation of pregnenolone and testosterone were inhibited dose-dependently with low nanomolar IC_{50} values (13 and 41 nM, respectively) in a cell line originating from hormonally active adrenocortical carcinoma (NCl-H295R) and expressing all the key enzymes for steroidogenesis and having the ability to produce all the adrenocortical steroids.

In intact mature male animals, oral ODM-208 showed exposure-dependent inhibition of steroid synthesis in all studied species (mouse, rat, dog and monkey). Changes in weight and histopathology of target tissues were observed in rats and dogs after repeated dosing. ODM-208 (oral administration twice daily) significantly inhibited tumour growth at well tolerated doses in the murine VCaP CRPC xenograft model, which overexpresses AR. Suppression of tumour growth by ODM-208 was enhanced by concomitant administration with prednisone, suggesting

benefit from combining corticosteroids with ODM-208 to decrease hypothalamic feedback to adrenals.

ODM-208 shows moderate bioavailability (68%) and low systemic clearance in dogs after intravenous administration. Bioavailability is moderate to high in rats (64-70%), and moderate in monkeys (22-55%). Systemic clearance is moderate in rat and low in dogs. In vitro cross-species comparison in hepatocytes suggests that metabolic clearance in human will be low.

In mice, rats and dogs concentration levels of ODM-208 were high in the adrenal gland. The concentration levels in the brain were low in the rat and dog (0.1-0.4 -fold of plasma concentration).

ODM-208 was rapidly absorbed in mice, rats, dogs and monkeys reaching maximum concentration in plasma (C_{max}) in general within 2 h. The ODM-208 elimination half-life in the rat, dog and monkey was 2.2-3.3h.

ODM-208 was not mutagenic in the bacterial reverse mutation test (Ames test) and no genotoxicity was seen in the in vitro and in vivo rat micronucleus assays.

Safety pharmacology studies with ODM-208 did not show any significant effects on central nervous system (CNS), respiratory or cardiovascular functions. The human Ether-à-go-go-Related Gene (hERG) assay did not indicate a risk of QT prolongation (46% inhibition at 100 µM) and sodium and calcium ion channels (hNav1.5 and hCav1.2) were inhibited only at high concentrations (100 µM).

To assess toxicity, repeated daily dosing was performed in rats and dogs for 14 and 28 days. Clear species difference in tolerability was seen after repeated dosing. When ODM-208 was administered without corticosteroid replacement, rats tolerated moderately high dose of ODM-208, whereas in dogs intolerability was observed already at relatively low doses of ODM-208. Inclusion of corticosteroid replacement therapy in dogs increased the tolerability and permitted repeated administration of ODM-208.

The toxicity of ODM-208 was manifested mainly as body weight loss, decreased food consumption and clinical signs (tiredness/decreased activity, dehydration, cold surface) in rats and dogs, and was considered to be related to ODM-208 effects on the adrenal gland function. Altered electrolyte levels and changes indicative of dehydration were seen in laboratory determinations. These effects were less severe and no clinical signs were seen in dogs when corticosteroid replacement therapy was combined with ODM-208. In the 28-day toxicity studies the main target organs identified for ODM-208 were endocrine glands and reproductive organs, with findings being present at all studied dose levels. The adrenal glands showed marked hypertrophy and vacuolation of the cortex, which recovered slowly. Hypertrophy was present in the pituitary (anterior part) and thyroid gland, and was associated with increased thyroid-stimulating hormone (TSH) levels in both species. Hypertrophy and vacuolation was seen in the steroid producing cells in the testes and ovaries, and was reflected as dose-dependent atrophy in hormone-dependent tissues (prostate). In addition, slightly increased bilirubin level was seen in both species without any histological changes in the liver. No clear difference was seen in the target organ pathology between dogs treated with or without replacement therapy. All changes showed full or partial reversibility after 4-8 weeks of treatment-free period and were mainly related to the pharmacologic action of ODM-208 (inhibition of the steroid synthesis). The mechanism behind the changes in thyroid gland and increased bilirubin remains unknown.

The nonclinical safety evaluation of ODM-208 has been conducted in accordance with the International Conference on Harmonisation (ICH) S9 guideline (EMA/CHMP/ICH/646107/2008).

The results of nonclinical studies suggested that ODM-208 may have therapeutic potential for treatment of men with advanced CRPC.

1.1.1 Clinical Data

By the data cut-off date Aug 06, 2020 of this study (3124001) a total of 38 patients with mCRPC have been treated in phase 1 (Part 1A and 1B). 5 dose levels of ODM-208 given twice daily and one dose level given once daily were studied: 5 mg twice daily (n=6), 25 mg once daily (n=3), 15 mg twice daily (n=4), 25 mg twice daily (n=3), 50 mg twice daily (n=19), and 75 mg twice daily (n=3). Three different glucocorticoid replacement regimens containing dexamethasone, hydrocortisone, or prednisone in combination with ODM-208 have been evaluated concomitantly with fludrocortisone replacement. The starting dose of ODM-208 was 100 mg (50 mg twice daily). The dose levels and replacement therapies tested are presented in Table 1.

Table 1. Subject disposition in Phase 1 (as of 06 Aug 2020)

Glucocorticoid replacement therapy[1]	Daily dose	ODM-208 daily dose[3]					
		5 mg b.i.d	25 mg q.d.	15 mg b.i.d.	25 mg b.i.d.	50 mg b.i.d.	75 mg b.i.d.
- Dexamethasone	1 - 1.5 mg	6	3	4	3	8	3
- Hydrocortisone	40 mg (n=3), 80 mg[2] (n=3)					6	
- Prednisone	5 - 20 mg					5	

[1]All subjects used fludrocortisone of 0.05-0.1 mg daily. [2]Higher dose was used from day 2 for the first 4 weeks, after that gradually tapered down to 40 mg of hydrocortisone or the equivalent dose. [3]The starting dose of ODM-208 was 50 mg b.i.d. The dose was escalated to 75 mg b.i.d., but de-escalated back to 50 mg b.i.d. due to DLTs. Doses were thereafter studied in the following order: 25 mg b.i.d., 25 mg q.d., 15 mg b.i.d. and 5 mg b.i.d.

ODM-208 was absorbed rapidly by most patients after oral dosing with food. Median time to plasma peak concentration (t_{max}) for ODM-208 was 1-4 hours after a single dose of ODM-208 5 mg, 15 mg, 25 mg, 50 mg or 75 mg. The exposure (area under the plasma concentration-time curve [AUC]) and C_{max} values after one-week of repeated dosing were about the same level as the corresponding values after a single dose of ODM-208.

Serum testosterone levels were reduced rapidly after a single dose of 5-75 mg of ODM-208. No dose-response relationship between the dose and testosterone decline was observed. Up to one week after repeated dosing of ODM-208, testosterone levels were reduced below the lower limit of quantification (LLOQ <0.2 ng/dl, 0.0069 nmol/l) at all dose levels. The testosterone levels remained below the LLOQ at 4 weeks in all evaluable patients (excluding one patient at 75 mg

~~b.i.d. with a temporary interruption of ODM-208 due to SAE), and at 12 weeks in all evaluable patients.~~

~~Adverse events (AEs) occurred in 36 patients (94.7%). 32 (84.2%) patients experienced at least one treatment-related AE including 14 patients (36.8%) with treatment-related grade 3 AE. Three patients died due to prostate cancer progression during the post-treatment period of the study. The most common treatment-related AEs were adrenal insufficiency in 13 patients (34.2%), fatigue in 8 patients (21.1%), hyponatremia in 6 patients (15.8%), amylase increased in 5 patients (13.2%), asthenia in 4 patients (10.5%), oedema peripheral in 4 patients, hyperkalaemia in 4 patients, muscle spasms in 3 patients (7.9%), decreased appetite in 3 patients, headache in 3 patients, hypertension in 3 patients and alanine aminotransferase increased and aspartate aminotransferase increased in 3 patients each. 20 patients (52.6%) experienced serious adverse events (SAEs). The most common SAE was adrenal insufficiency in 11 patients (28.9%). Glucocorticoid deficiency, which presumably reflects the same condition, occurred in one patient, and together with adrenal insufficiencies, these serious events occurred in a total of 12 patients (31.6%). The majority of the subjects experiencing adrenal insufficiency SAE were treated with high-dose i.v. hydrocortisone (1-2 days) and with temporary interruption of ODM-208 leading to a rapid improvement in the symptoms. The SAEs occurred typically 17 days after starting the study treatment (range 3 days – 56 days). The signs and symptoms of adrenal insufficiency included asthenia/fatigue, nausea, vomiting, abdominal pain, muscle cramps/pain, lowered serum sodium, elevated serum potassium, fever and elevated serum CRP.~~

~~mCRPC patients with or without identified activating mutation(s) in the AR LBD in plasma ctDNA were enrolled. A total of 6 out of 31 (19.4%) evaluable patients had a PSA response (≥ 50% decline from baseline). A clear difference in the frequency of PSA responses was seen between the patients with mutated AR LBD and the patients without AR LBD mutation. 4 out of 8 (50%) evaluable patients with activating mutation in the AR LBD had PSA response, and one of them achieved partial radiographic soft tissue response (PR) by RECIST 1.1. A total of 2 out of 23 (8.7%) evaluable patients without activating mutation in the AR LBD had PSA response, and in this patient group radiographic soft-tissue responses remained absent. The mean time on treatment in AR LBD mutation-positive patient group was 4.8 months, the longest treatment period was 26 months. No dose-response relationship between the ODM-208 dose and antitumour activity was observed.~~

For further details on ODM-208 and human data from the ongoing clinical study (3124001), see the current ODM-208 Investigator's Brochure.

1.2 Rationale of the study

1.2.1 Rationale of the study design

This first-in-human study has an open-label, non-randomised, uncontrolled design. Men with mCRPC who have received at least one prior line of novel hormonal AR targeted therapy (e.g. abiraterone, enzalutamide) can be enrolled into this study. This study has an integrated phase I-II study design and it is divided into 2 parts: a dose escalation part (Part 1) and a cohort expansion part (Part 2).

Part 1/Phase 1 is divided into 2 subparts: Part 1A and Part 1B. The primary objective of Part 1A is safety and tolerability. In Part 1A escalating dose levels of ODM-208 will be given to males

with mCRPC. A 3+3 rule-based design will be used in the dose escalation component. This design is commonly used in phase I oncology clinical studies for cytotoxic agents and molecularly targeted agents (Le Tourneau C et al., 2009). The principle of the design is that 3 patients are exposed to the first dose and if no patients experience dose limiting toxicity (DLT), the next 3 patients are treated at the next higher dose level. If 1 patient experiences a DLT, then the next 3 patients will receive the same dose level.

Part 1B is included to more accurately establish the recommended doses and dosing schedules of ODM-208 and the recommended corticosteroid replacement for further clinical evaluation, if needed. A dose(s) for Part 1B will be decided by safety monitoring board (SMB) based on data available from Part 1A.

In Part 1/Phase 1 prospective AR LBD mutation analysis in ctDNA (added in Amendment 6) may be used to select mutation positive patients who may be more likely to benefit from ODM-208 (based on currently available evidence in this 3124001 study).

Part 2/Phase 2 aims to further evaluate the safety, tolerability and preliminary antitumour activity of ODM-208 in patients with identified AR LBD mutation in plasma ctDNA by central testing. Presence of a defined activating mutation by central analysis (e.g. L702H, V716M, W742C, W742L, H875Y, F877L, T878A, T878S, M896T and M896V) at pre-screening is interpreted as a sign of AR LBD mutation positivity. The SMB will make a recommendation on Part 2/Phase 2 patient population based on the data available from Part 1/Phase 1.

The initial phase 2 expansion focussed on AR LBD mutation positive subjects in which a higher response rate was identified in Part 1. There were also some responses in the mutation negative subjects and, with a limited number of subjects, the underlying basis for those responses is not well understood. AR LBD mutations appear not to be the only basis for responding to ODM-208. The phase 2 expansion, introduced in Amendment 12, will thus be extended to achieve a cohort of approximately 60 subjects under phase 2 conditions with and without AR LBD mutations to permit more detailed analysis of the factors governing response to ODM-208, frequency of response, and to inform the design of the phase 3 program.

1.2.2 Rationale for selected doses

1.2.2.1 Part 1/ Phase 1

In the dose escalation part of this study, a starting daily oral dose was 100 mg of ODM-208 (50 mg twice daily). The starting dose is based on the data from the nonclinical pharmacodynamic (PD), PK and toxicity studies, including supporting data from the physiologically based pharmacokinetic (PBPK) and PK/PD modelling, and the ICH S9 guideline (EMA/CHMP/ICH/646107/2008) and Strategies to Identify and Mitigate Risk for First-in-human and Early Investigational Medicinal Products (EMEA/CHMP/SWP/28367/07 Rev. 1). The calculated starting dose is expected to have pharmacologic effects and to be safe to be administered in humans. Dog is considered the most sensitive animal model for the determination of starting dose of ODM-208.

Calculation of the starting dose of ODM-208 took into account the no-observed-adverse effect level (NOAEL) and the highest non-severely toxic dose (HNSTD) in male dogs, the severely

toxic dose in 10% of male rats (STD 10) in the 28-day toxicology studies, and the effective dose from the in vivo studies in a mouse CRPC xenograft model. The NOAEL in dog without replacement therapy was 2 mg/kg daily and HNSTD, when administered concomitantly with prednisone 2.5 mg/animal and fludrocortisone 0.1-0.15 mg/animal, was 10 mg/kg daily. 1/6th of the HNSTD as a starting dose (the human equivalent dose [HED]) in an 80-kg patient with an allosteric correction for the body surface area would be 72 mg daily. The NOAEL (without replacement therapy) corresponds to 87 mg daily HED for an 80-kg patient. In rat the dose level of 100 mg/kg/day was not tolerated and led to a decreasing of the dose during the study, and is, therefore, considered the STD 10. 1/10th of the STD 10 as the starting dose (HED) in an 80-kg patient with an allosteric correction for the body surface area would be 128 mg daily. A significant inhibition of tumour growth was observed in a mouse CRPC xenograft model at a dose of 20 mg/kg twice daily. The HED from a mouse xenograft model (40 mg/kg/day) for an 80-kg patient with an allosteric correction for the body surface area is 256 mg daily.

The starting daily dose of 100 mg of ODM-208 is slightly higher than the daily dose derived from NOAEL and 1/6th of the HNSTD in the dog (the HED 87 and 72 mg daily, respectively, for an 80-kg patient), but slightly lower than a 1/10th STD in the rat (a HED 128 mg for an 80-kg patient). The dose level of 100 mg is expected to be safe with concomitant corticosteroid administration and to have some pharmacological activity in human.

The dose level for Cohort 2 and all further cohorts in the dose escalation was decided by the SMB after a minimum of 3 patients on the previous dose level have provided evaluable data (see section 3.3.4). The dose escalation will be based on the review of PK, PD and safety data by the SMB and the maximum allowed incremental increase can be 100% in the absence of toxicity. Composition and further details regarding SMB are provided in section 10.1 and in the SMB charter.

The estimation of the maximum allowed exposure level in human is based on the data from the nonclinical studies in dogs and supporting data from the PBPK modelling. In safety pharmacology and toxicology studies, no adverse effects related to high C_{max} have been observed. The pharmacologic and toxicologic effects are considered more related to the total daily exposure of ODM-208 and long-lasting inhibition of steroid biosynthesis. Therefore, the AUC_{0-24} of ODM-208 is considered the most relevant PK parameter for consideration of maximum clinical exposure. In the 28-day toxicology studies in dogs the highest non-severely toxic dose level of ODM-208 when combined with replacement therapy (prednisone and fludrocortisone) was 10 mg/kg/day (432 mg daily HED for a 80 kg man). At this dose level, the highest achieved exposure level of ODM-208, AUC_{0-24}, was 36 500 h*ng/ml and did not produce any lethality, life-threatening toxicities or irreversible findings. The main target organ effect was hypertrophy and vacuolation in the adrenal glands, associated with minimal non-adverse changes in clinical pathology. In the preliminary 14-day dose range finding toxicology study in dogs the highest studied dose level with replacement therapy was 30 mg/kg daily (1300 mg daily HED for a 80 kg man), with AUC_{0-24} 76 000 h*ng/ml in a male dog. At this level adverse body weight loss (up to 11%) was seen, without any adverse clinical signs. Based on non-clinical data it is suggested that the highest achieved individual exposure with corticosteroid replacement therapy in the 28-day toxicology study in the dog is considered the initial maximum exposure level of ODM-208 in the human (AUC_{0-24} 36 500 h*ng/ml), which should not be exceeded in phase I dose escalation.

Twice daily dosing of ODM-208 was selected because the half-life of ODM-208 is expected to be relatively short in human based on nonclinical data and PBPK modelling. Extrapolations of

in vitro and in vivo data and allometric scaling of clearance from the nonclinical studies suggest that clearance and volume of distribution in human would result in a steady-state half-life of around 2-7 h, which is expected to be appropriate for twice daily dosing. Because of uncertainty in the translation of PK data from animal to human, the dosing condition may be changed during the study, if deemed appropriate by the SMB.

1.2.2.2 Part 2/Phase 2

The ODM-208 dose selected for Part 2 is 5 mg twice daily~~, which is the lowest dose level studied in Part 1/Phase 1~~. At this dose level, production of steroid hormones was as efficiently inhibited by ODM-208 as at the higher studied dose levels. In case 5 mg twice daily is not tolerated by a subject the dose may be reduced (for example by reducing dose frequency).

1.2.2.3 Concomitant treatment with corticosteroids

As inhibition of CYP11A1 is expected to result in glucocorticoid and mineralocorticoid deficiency, systemic glucocorticoid and mineralocorticoid substitution is required concurrently with ODM-208 treatment.

Dexamethasone was initially selected for testing of glucocorticoid replacement because it was expected to inhibit adrenocorticotropic hormone (ACTH) more effectively compared to hydrocortisone and prednisone due to its longer half-life. In clinical trials in patients with prostate cancer dexamethasone is usually used at doses of 0.5-1.5 mg daily (Narayanan S et al., 2016). Dexamethasone was selected to provide efficient inhibition of ACTH; a minimum of 1 mg starting daily dose of dexamethasone was used. Dexamethasone dose 1 mg daily is near the physiological dose and it is equivalent to prednisone dose of ~7 mg and hydrocortisone dose of ~27 mg.

1.2.2.3.1 Part 1/Phase 1

Hydrocortisone replacement therapy will also be evaluated (Part 1A Group 2 added in Amendment 3). According to the guideline of corticosteroid replacement therapy in patients with primary adrenal insufficiency, a daily dose of oral 15-25 mg of hydrocortisone divided into 2-3 doses is commonly used (Bornstein SR et al., 2016). In the ongoing clinical study (3124001) serious adverse events (SAEs) related to adrenal insufficiency have been observed during the first 2-3 weeks of the study treatment in patients with dexamethasone replacement with a daily dose level of 1 mg (see the current ODM-208 Investigator's Brochure). Treatment with ODM-208 is expected to cause chemical adrenalectomy as well as depletion of extra-adrenal steroid biosynthesis, and therefore a more robust glucocorticoid replacement than in patients with primary adrenal insufficiency is required. The minimum daily starting dose 40 mg of hydrocortisone divided into 3 doses was initially selected.

Replacement therapy (dexamethasone and/or prednisone/prednisolone and/or hydrocortisone) with a higher daily dose of glucocorticoid than the equivalent of 40 mg of hydrocortisone will be tested in order to minimise risk of adrenal insufficiency during the first weeks of study treatment. The higher glucocorticoid dose is recommended to be used at least during the first 4 weeks of the treatment with ODM-208. After that, the dose of a glucocorticoid is recommended to be reduced gradually and cautiously to a level which is deemed sufficient to replace the physiological need. For cohorts with high starting dose of glucocorticoid replacement therapy see examples in Appendix 3 (Added in Amendment 4).

Fludrocortisone is usually recommended for mineralocorticoid substitution as a single oral morning dose of 0.05-0.2 mg (Quinkler M et al., 2015). A daily dose of 50 µg was selected as a starting dose with glucocorticoid treatment. Fludrocortisone replacement therapy will be monitored during the study and the dose can be adjusted, if clinically indicated.

1.2.2.3.2 Part 2/Phase 2

Dexamethasone 1.5 mg (Amendment 12) and fludrocortisone 100 µg as single oral doses every morning will be ~~used as~~recommended replacement therapy starting doses. Dexamethasone was considered to be the most optimal replacement therapy in patients with AR LBD activating mutation and the safety profile of different glucocorticoid replacement therapies with ODM-208 appeared to be similar based on the results from phase 1 of this study. The increased dexamethasone recommended starting dose in Part 2 is to determine whether the higher dose more effectively reduces signs of adrenal insufficiency.

The replacement therapy will be closely monitored during the study and both starting and individual doses can be adjusted, if clinically indicated as judged by the SMB or investigator. Patients and investigators will be instructed in recognising early signs of adrenal insufficiency and how to adjust treatment accordingly.

1.3 Benefit-risk assessment

1.3.1 Potential benefits associated with ODM-208

Nonclinical studies have demonstrated antitumour activity in both in vivo and in vitro CRPC models. In Part 1/Phase 1 of this study, antitumour activity of ODM-208 has been observed in patients with mCRPC, especially (but not exclusively) in patients with mutated AR LBD in plasma ctDNA. Durable antitumour responses have been reported in some patients with the mutated AR LBD with one patient ongoing treatment for more than 2 years ~~(see Section 1.1.2)~~. Based on the mode of action it may be expected that any patient whose cancer is substantially dependent on steroid hormone (whether testosterone or another steroid ligand) may gain benefit from ODM-208 and AR LBD mutations appear not to be the only determinants of such hormone dependence in these patients.

Based on the available human, nonclinical pharmacology and toxicology data of ODM-208, it is considered that the potential benefit from ODM-208 treatment for patients with advanced CRPC progressed after novel AR targeted and chemotherapy treatments exceeds the risks.

This study builds on the accumulating data from Parts 1 and 2 on the management of adrenal insufficiency and serves as preliminary evidence of the clinical benefit, safety and tolerability of ODM-208 in the treatment of the AR LBD mutation positive and negative patient populations.

1.3.2 Identified and potential risks associated with ODM-208

Based on data from nonclinical studies and mechanism of action of ODM-208, a number of potential risks can be anticipated. It is expected that the main toxicities upon repeated dosing of ODM-208 will be adrenal insufficiency and further, an adrenal crisis, hypertrophy of steroid producing cells in testes, and atrophy of prostate. The clinical symptoms of adrenal insufficiency include weakness, fatigue, anorexia, abdominal pain, weight loss, orthostatic hypotension, salt craving and nausea (Charmandari E et al., 2014). The clinical symptoms of an adrenal crisis

includes fever, pain in the lower back, abdominal pain, severe myalgia, severe vomiting and diarrhoea, a low blood pressure (BP) and loss of consciousness (Arlt W et al., 2016). Glucocorticoid and fludrocortisone replacement therapy will be started for all patients to avoid adrenal insufficiency and symptoms related to insufficiency (see section 1.3.3). Prolonged suppression of the adrenal glands may lead to adrenal gland atrophy that may take from a few weeks to several months to recover, therefore after discontinuation of ODM-208 treatment a continuation of the replacement therapy is likely to be required for several weeks. In this study adrenal recovery will be followed up after discontinuation of ODM-208 (see section 6.1.6.3).

In addition, a repeated dosing of ODM-208 in nonclinical studies was associated with thyroid gland hypertrophy and increased TSH level. All these changes were reversible in animals. TSH levels will be monitored during the study and thyroid replacement will be started if clinically indicated. ~~By the data cut-off date Aug 06, 2020 of this study~~In the ongoing study, no clinically significant changes in TSH have been observed.

Adrenal insufficiency has been recognised as an important identified risk for ODM-208. In part 1/phase 1 of this study, the symptoms and signs of adrenal insufficiency have included asthenia/fatigue, nausea, vomiting, abdominal pain, lowered serum sodium levels, elevated serum potassium levels, fever, and elevated serum CRP. Benefit risk ratio of continuing ODM-208 treatment should be carefully considered in patients with recurring adrenal insufficiency event. In Part 2, the frequency of adrenal insufficiency has been lower than during Part 1, likely reflecting the low ODM-208 dose and more effective management of adrenal hormone replacement, including the increased fludrocortisone starting dose, although many patients have required dexamethasone dose increase for signs of adrenal insufficiency.

Based on suspected unexpected serious adverse reaction (SUSAR) reports received, rash and drug induced pneumonitis have been identified as potential risks. Anaemia and elevation of blood hepatic enzymes and lipids were identified risks in the non-clinical studies.

1.3.3 Potential risk associated with replacement therapy

Inhibition of CYP11A1 is anticipated to lead to deficiency in production of glucocorticoids and mineralocorticoids. Replacement therapy with glucocorticoid and mineralocorticoid is thus required with ODM-208 treatment.

It is expected that a significant proportion of patients have received corticosteroids for extended duration before entry to this study. Long-term use of moderate or high-dose corticosteroid doses (e.g. ≥ 20 mg prednisone daily) has a well-described adverse event (AE) profile including immunosuppression, hyperglycemia, myopathy, hypertension, osteoporosis, cataract, glaucoma, dyslipidemia, gastritis, and mood changes. Retrospective analyses of 2267 patients from phase III studies (COU-301-AA and COU-302-AA) showed that overall incidence of corticosteroid-associated AEs were low in mCRPC patients who used prednisone 5 mg twice daily with or without abiraterone. The most common AEs were hyperglycemia and weight increase. The frequency of corticosteroid-associated AEs remained low with increased duration of exposure to prednisone (Fizazi K et al., 2016). After discontinuation of the ODM-208 treatment, the glucocorticoid therapy will be gradually decreased with monitoring for adrenocortical insufficiency (see section 3.3.6.1).

To minimise risks related to over- or under-replacement with fludrocortisone close monitoring during the study will be done e.g. by measuring blood pressure (BP), serum electrolytes and

renin. If the dose is too low the patient might experience fatigue, postural hypotension/orthostatic dizziness, dehydration, hyperkalaemia and salt craving or if the dose is too high, the patient may experience hypertension, oedema/fluid retention, rapid weight gain and hypokalemia. Fluid retention and hypertension caused by hyperaldosteronism might lead to worsening of heart failure. After discontinuation of the ODM-208 treatment, the fludrocortisone therapy will be gradually decreased to avoid symptoms associated with mineralocorticoid deficiency.

1.3.4 Potential risks associated with the study assessments

Blood samples will be collected for safety laboratory assessments, PK, PD, biomarker, pharmacogenetic (PG) and metabolite screening analyses. The volume of blood collected from a patient over the first 3 months is not expected to exceed 450 ml. The risks of blood sampling include fainting and pain, bruising, swelling and rarely infection of the injection site.

Electrocardiogram (ECG) pads can cause skin irritation and the removal of the pads may be painful.

Exposure to ionising radiation may cause a small increase in a patient's lifetime risk of developing cancer. Computed tomography (CT) utilises ionising radiation in the form of X-rays. Estimated exposure varies depending on the part of the body being imaged, being 7 mSv (Mettler FA, Jr. et al., 2008) in a chest CT scan. The worldwide yearly average effective dose per person caused by natural sources is 2.4 mSv (UNSCEAR report, 2000). The amount of radiation the patient will be exposed to in bone scan is considered minimal.

As part of the CT and magnetic resonance imaging (MRI), an intravenous or oral contrast agent used during imaging may cause a rash with or without itching, swelling or other allergic reactions, including difficulty in breathing and decrease of BP or other general symptoms. Stomach cramps, diarrhoea, nausea, vomiting, and constipation may also occur. Patients who are claustrophobic (fear of enclosed spaces) may feel some anxiety while positioned in the MRI scanner.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objectives of this first-in-human study are

in Part 1/Phase 1 to:

- evaluate the safety and tolerability of ODM-208 in patients with mCRPC,
- define the maximum tolerated dose (MTD) and DLTs of ODM-208, if possible,
- define the recommended dose of ODM-208 for Part 2 of the study,

in Part 2/Phase 2 to:

- further evaluate the safety and tolerability of ODM-208,

- further evaluate the antitumour activity of ODM-208 in mCRPC patients with and without mutated AR LBD who have progressed after novel AR targeted therapy and taxane-based chemotherapy.

2.2 Secondary objectives

The secondary objectives of this study are

in Part 1/Phase 1 to:

- characterise the PK of ODM-208 after single and repeated administration,
- evaluate dosing schedule of ODM-208,
- evaluate the preliminary antitumour activity of ODM-208.

in Part 2/Phase 2 to:

- evaluate different AR LBD activating mutations and their association with antitumour activity of ODM-208.

2.3 Exploratory objectives

The exploratory objectives of this study are:

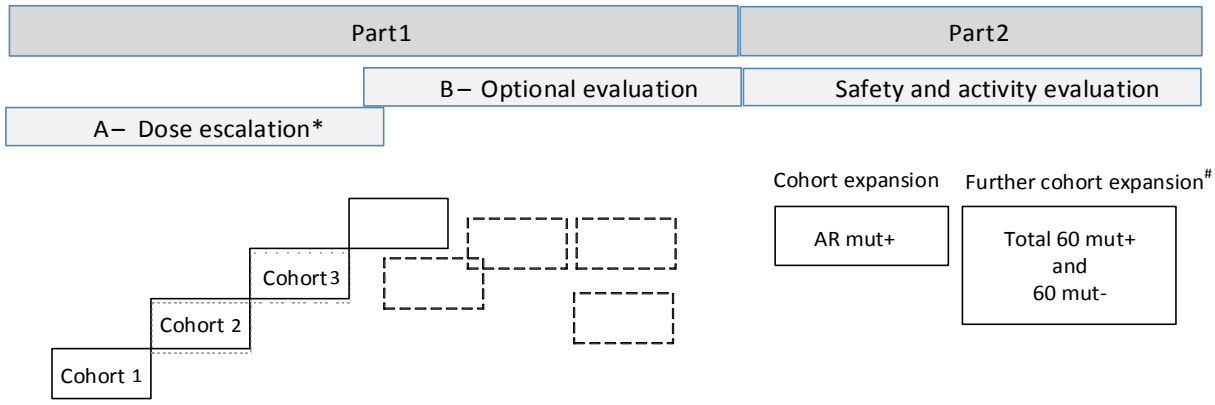
- to evaluate the relationship between AR-V7 splicing variant and antitumor activity of ODM-208 (Part 2/Phase 2 only),
- to evaluate the relationships between ODM-208 dose, plasma exposure and PD markers and safety,
- to study molecular biomarkers at genomic, protein and metabolite level from plasma/serum if feasible for clinical response to ODM-208 and target inhibition,
- to assess relationship between germline genetic polymorphisms and PK, PD, clinical response, and safety of ODM-208, if relevant.

3. OVERALL STUDY DESIGN AND PLAN

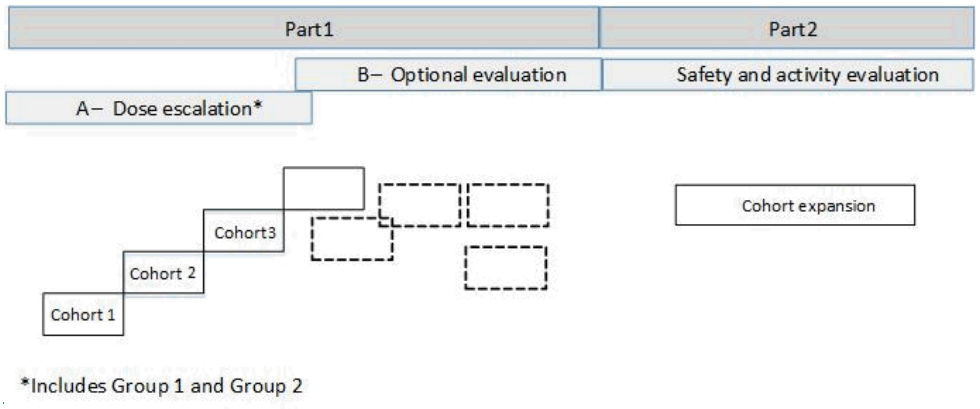
This is an open-label, non-randomised, uncontrolled, multicentre, first-in-human integrated phase I-II study containing a dose escalation part (Part 1A), an optional part for further evaluation of dosing of ODM-208 and evaluation of corticosteroid replacement therapy (Part 1B), and a cohort expansion part (Part 2).

The overall study design is presented in Figure 1.

Figure 1. Overall study design



*Includes Group 1 and Group 2
#Total includes 45 AR mut+ subjects already enrolled in Part 2. (added in Amendment 12)



*Includes Group 1 and Group 2

Part 1/Phase 1 of the study consists of a screening period of maximum 21 days, a treatment period for each patient lasting as long as it is considered beneficial to the patient (as judged by the investigator) or until death, intolerable toxicity, or any other discontinuation criteria is met, and a post-treatment period (28 days). If needed, adrenal recovery will be followed after the end-of-study visit (EOS) (for a maximum of 24 weeks) (added in Amendment 3). In addition, the study consists of an optional pre-screening period for a mutation analysis of the AR gene.

While on study treatment, patients will visit the site once a week for the first 4 weeks, every 2 weeks from week 4 to week 12, every 4 weeks from week 12 to week 24, and thereafter every 12 weeks until discontinuation of study treatment. Weekly telephone contacts (TCs) are included for the first 4 weeks. During the post-treatment period after the discontinuation of the ODM-208 treatment, adrenal recovery of the patients will be followed by weekly visits until EOS. If the

patient is still on corticosteroid replacement therapy at EOS visit, adrenal recovery of the patient will be followed by a visit at 4 weeks and, if needed, at 8 weeks. If replacement therapy still needs to be continued beyond 8 weeks after the EOS, the patient will be contacted by a phone call at 16 weeks and, if needed, at 24 weeks after the EOS. Visit schedule for Part 1 is presented in Figure 2. The DLT period in Part 1 is 28 days (section 3.3.4).

Part 2/Phase 2 of the study consists of a pre-screening period (≤ 3 months prior to screening start) for centralized analysis of the AR LBD mutations in plasma ctDNA, a screening period of maximum 21 days, a treatment period for each patient lasting until disease progression or until death, intolerable toxicity, or any other discontinuation criteria is met. The treatment may be continued after disease progression if the patient is considered to clinically benefit from the treatment as judged by the investigator. The study contains a post-treatment period (28 days), and if needed, adrenal recovery will be followed after the end-of-study visit (EOS) (for a maximum of 24 weeks).

While on study treatment, patients will visit the site once a week for the first 4 weeks, every 2 weeks from week 4 to week 12, every 4 weeks from week 12 to week 24, and thereafter every 12 weeks until discontinuation of study treatment. Telephone contacts (TCs) are included for the first 7 weeks. During the post-treatment period after the discontinuation of the ODM-208 treatment, adrenal recovery of the patients will be followed by a visit taking place 2 weeks after the treatment discontinuation. The EOS visit takes place 4 weeks after the discontinuation of the ODM-208. If the patient is still on corticosteroid replacement therapy at EOS visit, adrenal recovery of the patient will be followed by a visit at 4 weeks and, if needed, at 8 weeks. If replacement therapy still needs to be continued beyond 8 weeks after the EOS, the patient will be contacted with a phone call at 16 weeks and, if needed, at 24 weeks after the EOS. Patient survival status will be checked at least every 12 weeks, by telephone, e-mail, chart review, or review of public records, in compliance with local practices or regulations, for up to 2 years after the EOS visit for the final patient. Visit schedule for Part 2/Phase 2 is presented Figure 3.

Figure 2. Visit schedule for Part 1/Phase 1.

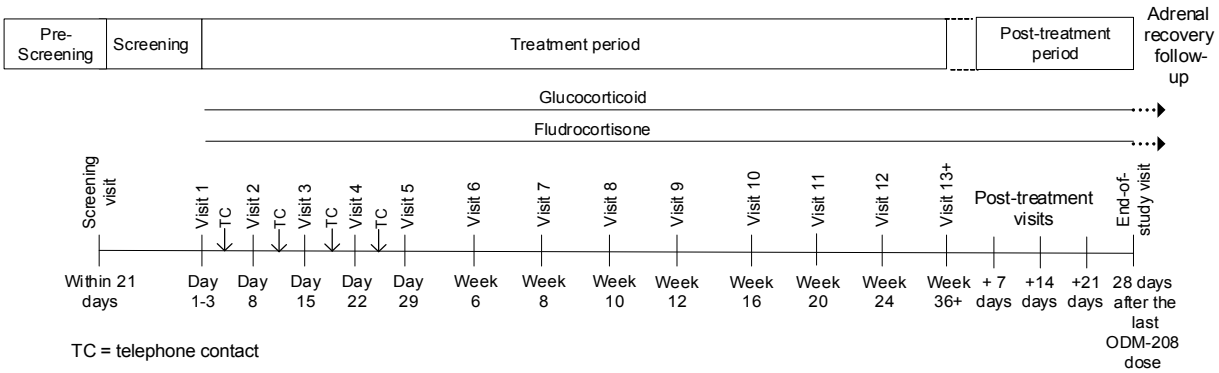
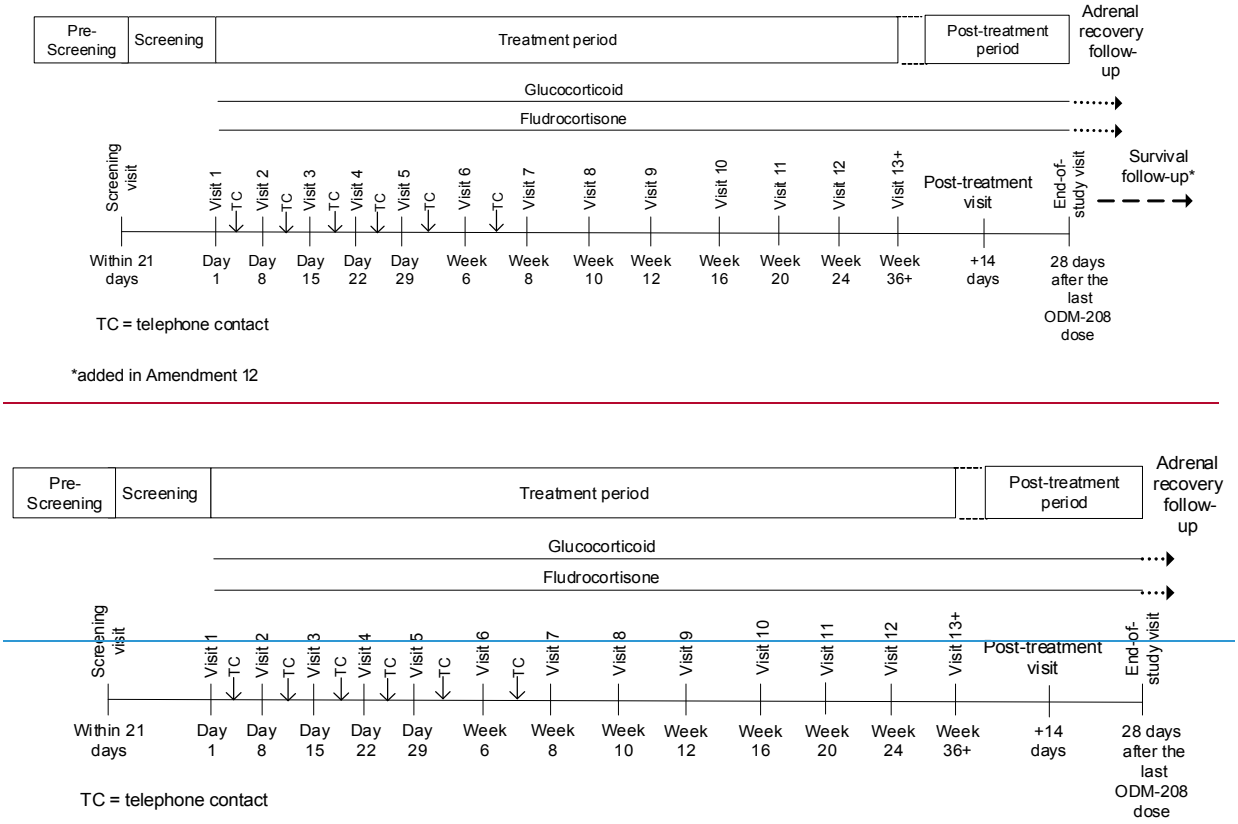


Figure 3. Visit schedule for Part 2/Phase 2.



3.1 Part 1/Phase 1: Dose escalation and dosing evaluation

3.1.1 Dose escalation (Part 1A)

Part 1A Group 1 ODM-208 and replacement therapy with dexamethasone and fludrocortisone

The starting total daily oral dose is 100 mg ODM-208 (50 mg twice daily). In the morning of Day 1 (Visit 1), a single dose of ODM-208 is given with food concomitantly with a minimum of oral dexamethasone 1 mg, and fludrocortisone 50 µg per day followed by (after 24 h) twice daily repeated dosing of ODM-208 and dexamethasone and fludrocortisone once daily.

Part 1A Group 2 ODM-208 and replacement therapy with hydrocortisone and fludrocortisone (added in Amendment 3)

The starting total daily oral dose for Group 2 is 100 mg ODM-208 (50 mg twice daily) with a minimum of daily dose of 40 mg of hydrocortisone, and fludrocortisone 50 µg per day (Amendment 4). In the morning of Day 1 (Visit 1), a single dose of ODM-208 is given with food

concomitantly with oral hydrocortisone and fludrocortisone. The 2nd oral hydrocortisone dose will be taken in the afternoon and the 3rd oral hydrocortisone dose in the evening. 24 hours after a single dose, repeated twice daily dosing of ODM-208 with hydrocortisone three times daily and fludrocortisone once daily, will be started.

Escalating doses of ODM-208 will be administered in cohorts of 3 to 6 patients based on 3+3 study design.

Dosing of the second patient in each dose escalation cohort can start after the first patient in the cohort has completed at least 14 days of repeated dosing. Dosing of subsequent patients in the same cohort can start from at least 24 h after the dosing of the previous patient. Before start of dosing of the second patient in each cohort, the safety data of the first patient from the first 14-day treatment period will be evaluated in a teleconference including the investigator from the study centre where the patient is enrolled and the SMB support group (see section 10.1.2). The principal investigators from the other study centres may attend the teleconference, but their attendance is not mandatory for quorum. Before start of dosing of the third patient in each cohort, medical monitor will contact the investigator from the study centre where the second patient is enrolled to confirm that no signs of DLTs have emerged.

The dose level for Cohort 2 and all further cohorts will be decided by the SMB after a minimum of 3 patients have provided evaluable data from 28-day treatment period on the previous dose level, as defined in section 3.3.1.

Patients can continue with repeated administration of ODM-208 at the same dose level until 12 weeks, after which the dose increases are allowed (see section 3.3.5.1.1).

3.1.2 Optional evaluation of ODM-208 and replacement therapy dosing regimen (Part 1B)

Part 1B may be conducted if further evaluations on the dosing or the dosing conditions of ODM-208 are considered to be needed based on data from the study. Such evaluations might include further assessment of the type and the dose of corticosteroid replacement therapy or alternative ODM-208 doses, if supported by the emerging data from the ongoing Phase 1 component. For example, replacement therapy with a higher daily dose of a glucocorticoid than the equivalent of 40 mg of hydrocortisone (dexamethasone and/or prednisone/prednisolone and/or hydrocortisone) may be evaluated.

Part 1B may start before Part 1A is completed. Studied doses and dosing schedules of ODM-208 should provide exposure that is considered safe and tolerable based on information from Part 1A, and does not exceed highest safe dose level of ODM-208 in Part 1A. The doses of ODM-208 and replacement therapy will be recommended by the SMB. In Part 1B, ODM-208 will be administered in cohorts of 3 to 6 patients to explore, for example, intermediate or lower dose levels of ODM-208 (under 50 mg twice daily), different dosing conditions or other factors affecting bioavailability, e.g. dosing of ODM-208 without food. If ODM-208 plasma exposures in different dosing conditions e.g. without food or once daily remain significantly lower compared to dosing with food or twice daily in Part 1A, dosing condition can be changed after 4 weeks.

The SMB can decide to further expand any cohort by up to 6 additional patients (i.e. up to 12 patients at a dose level) if this is considered important to support the objectives of the study

(to have more data prior determination of stratification group(s) e.g. from post-abiraterone patients and of replacement therapy).

Patients can continue with repeated administration of ODM-208 at the same dose until 8 weeks, after which the dose increases are allowed (see section 3.3.5.1.1).

3.2 Part 2/Phase 2: Expansion

Part 2 will be conducted to further evaluate the safety, tolerability, and preliminary antitumour activity. The dose level of ODM-208 for expansion has been recommended by the SMB. After an initial expansion of approximately 40 mCRPC patients with AR LBD mutations, Part 2 will be further expanded to create cohorts of approximately 60 patients with (see section 1.2.1) and approximately 60 mCRPC patients without mutated AR LBD.~~After completion of the dose escalation in Part 1A, Part 2 with expanded cohort of up to 40 mCRPC patients with mutated AR LBD (see section 1.2.1) will be enrolled.~~ The ODM-208 dose level is 5 mg twice daily with recommended concomitant replacement therapy of 1.5 mg dexamethasone and 100 µg of fludrocortisone once daily. Lower doses of ODM-208 (including reduced dosing frequency) may be considered if the patient does not tolerate the intended dose and such lower dose has been evaluated in study Part 1.

3.3 Procedures and criteria for dosing in Part 1/Phase 1 and Part 2/ Phase 2

3.3.1 Criteria for dose escalation in Part 1A

All cohorts will consist of a minimum of 3 patients, potentially expanded to 6 patients for determination of MTD.

If 1 of the first 3 patients experiences DLT (see section 3.3.4), 3 more patients will be treated at the same dose level (3+3). If no further DLTs are observed, dose escalation may proceed. However, if a further DLT is observed in the same cohort (2 or more patients, i.e. ≥ 33% of patients) dose escalation will be discontinued. MTD is defined as the highest dose level at which < 33% of patients in a cohort experience DLT.

3.3.2 Summary of decisions made by the SMB in Part 1/Phase 1

The SMB can make decisions regarding:

- Further dosing in the study after a minimum of 3 patients have provided evaluable DLT data, as defined in section 3.3.1.
    - addition of 3 patients to a cohort.
    - continuation of dose escalation.
- Discontinuation of dose escalation due to achieved MTD, PK plateau of ODM-208 exposure, PD plateau or other reasons.
- The dose of ODM-208, administration regimen and dosing conditions for every dose level. Recommendation on corticosteroid replacement therapy.

- Changes in timepoints and the number of PK sampling points, and safety and PD assessments without exceeding total allowed blood amount taken.
- Replacement of patients not providing evaluable data for DLT.
- Addition of cohorts at intermediate dose level and/or addition of patients to already studied dose levels and the number of patients in these cohorts.
- Inclusion of additional safety cohorts after completion of dose escalation and number of patients to be studied.
- Start of Part 1B and Part 2.
- Recommendation for dose of ODM-208 for Part 2.

More detailed instructions are provided in the SMB charter.

3.3.3 SMB in Part 2/Phase 2

Periodic safety data evaluations will be performed during Part 2/Phase 2 by the SMB according to instructions in the separate SMB charter.

3.3.4 Dose Limiting Toxicity (DLT)

The DLT period is defined as the first 28 days of study treatment. The patient is considered evaluable if ODM-208 is administered at a compliance level greater than 80% of DLT period (i.e. at least 23 days).

A DLT is defined as any of the following toxicities (grading according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE ver. 4.03 https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

assessed as related to ODM-208 and occurring during the DLT period.

- Grade ≥ 3 haematological toxicity lasting for ≥ 7 days.
- Persistent nausea, vomiting or diarrhoea of grade ≥ 3 despite optimal medical intervention (not used as a prophylactic regimen).
- Other grade ≥ 3 toxicities of any duration, except grade 3 or 4 laboratory findings that are not considered clinically significant by the investigator.

Any toxicity that meets the above mentioned DLT criteria but is assessed by the investigator to be related to sub-optimal level of replacement treatment, and which recovers within a week after adjusting the dose of replacement treatment is not considered a DLT, if SMB decides so after careful assessment of the case. However, in these cases, a total of 6 patients must be treated at the dose level in question before dose escalation can proceed.

Any AE, which in the opinion of the investigator and sponsor is unrelated to study treatment, will not be considered a DLT.

3.3.5 Criteria for dose interruption and resuming, or modification

3.3.5.1 ODM-208 treatment

If ODM-208 needs to be interrupted for any reason, administration of replacement treatment must be continued. If dosing is interrupted for more than 14 days, the patient should discontinue ODM-208 treatment. Patients who experience treatment related toxicity must be observed until resolution or stabilisation of the AE to grade 1 or baseline.

Part 1/Phase 1

If a patient experiences a DLT, no further doses will be administered to this patient until resolution of the toxicity to grade 1 or baseline. Dosing at the next lower dose may be pursued if considered beneficial to the patient and approved by the medical monitor and the sponsor. If the patient experiences a DLT at the lower dose level, ODM-208 dosing should be permanently discontinued.

Patients who have interrupted ODM-208 treatment due to toxicity not meeting DLT criteria and recovered from treatment related toxicity may resume ODM-208 treatment at the same or lower dose level after careful assessment of the nature and course of the toxicity, and extent of resolution by the investigator and the medical monitor. Once the dose has been reduced for a patient, ODM-208 treatment will be continued at the modified dose unless further dose reduction is required.

3.3.5.1.1 ODM-208 dose increase in Part 1A and 1B after 8 weeks treatment

In Part 1, intra-patient dose escalation is not permitted during the first 8 weeks. After that, the ODM-208 dose may be increased at the time of disease progression at the discretion of the investigator. The medical monitor should be contacted before dose increase. The dose may be increased to the highest tolerated dose in dose escalation, as determined by the SMB, achieved at the time of progression. The dose may be increased to the highest tolerated dose at once or in steps. If no disease stabilisation or improvement is observed at the higher dose level at the discretion of the investigator, the patient should discontinue the study treatment.

3.3.5.2 Dose modifications of corticosteroids

3.3.5.2.1 Dose modification of glucocorticoid and mineralocorticoid replacement therapy due to under-replacement

The early identification of inadequate replacement therapy is essential for the safety of patients in the study. Guidance on the management of adrenal insufficiency is presented in Appendix 2A and measures to prevent adrenal crisis in Appendix 2B. Further, the IC and the diary contain guidance for the patient when to contact the study personnel in the event of possible symptoms. Study personnel will receive training from an endocrinologist at the start of the study in identifying and treating possible adrenal insufficiency and a flowchart is provided to guide clinical decision-making (see Appendix 2C, added in Amendment 7). Moreover, the fludrocortisone starting dose will be increased to 100 µg in Phase 2. The digital symptom questionnaire (see section 6.5.4.7) will be trialled in the first 40 patients enrolled in Part 2 as a possible means to identify early indications of inadequate replacement therapy in future studies (note: the digital symptom questionnaire will not be used in France) but not in subsequent

patients. An emergency kit is also provided to each patient for emergency use in case of suspected adrenal crisis.

For safety reasons and if clinically indicated, dose adjustment including changes in dosing frequency of replacement therapy or switch to another glucocorticoid may be done at the discretion of the investigator.

During periods of increased stress, such as mild/moderate illness/flu (fever under 38°C), pain, strenuous physical activity, hot weather, accident, emotional stress, where an increase in endogenous cortisol is needed, the replacement therapy dosing may be inadequate. Patients will be instructed that on the first signs of illness they should immediately take an additional dose of steroid replacement therapy and subsequently contact the investigator for further guidance. If the patient cannot take the steroid replacement for any reason, such as vomiting, they should seek immediate hospital care for parenteral steroid replacement.

An inadequate dose of glucocorticoid may lead to typical signs of under-replacement including weight-loss, fatigue, lack of energy, nausea, myalgia, leg cramps, poor appetite, hypotension, and hyponatremia. Acute warning signs of the adrenal crisis include hypotension (particularly postural hypotension), shock, and hyponatremia.

Salt craving, fatigue, postural hypotension/dizziness, dehydration, hyponatremia and hyperkalaemia indicate too low dose of mineralocorticoid. Elevated blood renin activity or concentration supports the clinical diagnosis. If signs of under-replacement are observed, dose increase of fludrocortisone needs to be considered. Temporary fludrocortisone dose increments of 50-100% or increased salt intake may be needed in a hot climate on conditions that promote excessive sweating.

Monitoring of replacement dose is mainly based on the clinical assessments of patient's symptoms and the clinical status including the weight, the BP and electrolytes. Patients and their family members should be educated for the event of possible acute or chronic signs of under-replacement. If corticosteroid deficiency is suspected to occur, patients should contact the study site without delay for additional instructions including follow-up and management plan. The study personnel should have a low threshold to suspect adrenal insufficiency, in order to prevent development of adrenal crisis. Additional replacement (doubled or tripled the dose of glucocorticoid and/or increased fludrocortisone dose and/or increased consumption of electrolyte containing fluids) should be considered whenever the patient reports persisting, new or worsened symptoms or signs above or in the event of unexplained electrolyte disturbance or has concurrent illness or injury. Acute illness or illness should routinely lead to temporary increases in replacement doses. An unscheduled follow-up visit including further symptom and clinical status evaluation, weight, BP, and electrolytes may be required. If the condition deteriorates despite these actions, or if the absorption of the replacement therapy is inadequate, such as during vomiting and diarrhoea, the patient should be instructed to use the emergency kit with parenteral (intramuscular) hydrocortisone according to institutional hospital guidelines or instructions provided by the sponsor. If the injection of parenteral hydrocortisone remains unsuccessful or impossible, up to 10 oral hydrocortisone tablets (10 mg), provided in the emergency kit, can be used in these situations as emergency. Immediately after the use of the emergency kit the patient must seek emergency hospital care. Patients with acute illness and fever over 38°C should always be admitted to the hospital directly.

Patients should carry steroid emergency card stating that they take glucocorticoid and mineralocorticoid daily. It is recommended that patients keep a small supply of glucocorticoid medication with them at all time.

Part 1 only: The higher daily dose of a glucocorticoid than the equivalent of 40 mg of hydrocortisone is recommended to be used at least during the first 4 weeks of the treatment with ODM-208. After that, the glucocorticoid dose is recommended to be decreased gradually and cautiously to a level which is deemed sufficient to replace the physiological need (e.g. to the equivalent of 15 mg – 40 mg hydrocortisone per day, see Appendix 3) (Amendment 4).

3.3.5.2.2 Dose modification of glucocorticoid and mineralocorticoid replacement therapy due to over-replacement

For safety reasons and if clinically indicated the dose of replacement therapy may be reduced by the decision of the investigator if over-replacement is suspected to have occurred.

The signs and symptoms of over-replacement of glucocorticoid include weight gain, peripheral oedema, hypertension, insomnia, impaired glucose tolerance and hyperglycemia.

The signs and symptoms of over-replacement of mineralocorticoid include hypertension, rapid weight gain, oedema/fluid retention, hypokalaemia, and low plasma renin.

All dose interruptions and modifications must be recorded on case report forms (CRFs).

3.3.6 Duration of ODM-208 treatment and corticosteroid replacement

Patients can continue to receive ODM-208 treatment concurrently with corticosteroid replacement until disease progression or as long as it is considered clinically beneficial to the patient (as judged by the investigator) and no new anticancer treatment is initiated or until death, unacceptable toxicity, or any other discontinuation criterion is met, whichever occurs first.

3.3.6.1 Discontinuation of replacement therapy

The time needed to taper down corticosteroids is individual and depends on the duration of adrenal gland suppression. Prolonged suppression may lead to adrenal gland atrophy that may take from a few weeks to several months to recover. Tapering down replacement therapy will be monitored during post-treatment period (see Section 6.1.6).

The glucocorticoid and mineralocorticoid replacement therapy should be withdrawn gradually and with caution avoiding secondary adrenal insufficiency.

The patient will be instructed that during stressful situations, such as fever, infection, trauma, surgery or mental stress, the glucocorticoid replacement dosing may be inadequate and extra substitution may be needed (information included in the IC and the diary).

3.3.7 Definitions of tumour response and disease progression

Assessment of disease progression during the study will be based on PSA, imaging and clinical status. A change in tumour burden will be assessed using the Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 (Eisenhauer EA et al., 2009). Status of bone will be assessed using

the Prostate Cancer Working Group 3 (PCWG3) criteria (Scher HI et al., 2016). PSA response and progression will be evaluated using the PCWG3 criteria.

Clinical disease progression is characterised by e.g. an increase in patient's Eastern Cooperative Oncology Group (ECOG) score, clinically significant loss of appetite, weight loss (more than 10% from baseline), or increase in pain and it refers to cases where the clinical deterioration of a patient is judged to be due to tumour progression that cannot be documented using objective methods. Such cases should be carefully differentiated from disease-related AEs, ODM-208-related and corticosteroid-associated symptoms and signs. The decision regarding disease progression is made by the investigator based on available data.

Part 2/Phase 2 only: CTC response is defined as CTC count nonzero at baseline and 0 at 12 weeks (CTC0) (Heller G et al., 2018).

4. SELECTION OF STUDY POPULATION

4.1 Number of patients

The expected number of patients to be enrolled into the study:

Part 1A: Maximum 36 patients with mCRPC

Part 1B: Maximum 36 patients with mCRPC

Part 2: Goal is to have approximately 640 mCRPC patients with mutated AR LBD and approximately 60 AR LBD mutation negative mCRPC patients.

No formal sample size calculation was performed.

4.2 Inclusion criteria

Subjects must meet all of the following criteria to be eligible for the study:

1. Written informed consent (IC) obtained.
2. Males aged ≥ 18 years.
3. Life expectancy > 3 months.
4. ECOG performance status 0-1.
5. **For Part 1/Phase1:** Histologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features. **For Part 2/Phase 2:** Histologically confirmed adenocarcinoma of the prostate without pure small cell features.
6. Metastatic disease documented either by a positive bone scan, CT, PET/CT or MRI scan.
7. Castration-resistant prostate cancer with serum testosterone < 50 ng/dl (< 0.5 ng/ml, < 1.7 nmol/l).
8. Patients must maintain ongoing androgen deprivation therapy with a gonadotropin-releasing hormone (GnRH) analogue (agonist or antagonist) or have had bilateral orchiectomy.

9. **For Part 1/Phase 1:** Treatment with at least 1 line of chemotherapy or ineligibility for chemotherapy. **For Part 2/Phase 2:** Treatment with at least 1 line of taxane-based chemotherapy in castration-sensitive prostate cancer (CSPC) or in CRPC.
10. Treatment of at least 1 line of novel AR targeted hormonal therapy in CSPC or in CRPC for a minimum of 12 weeks (e.g. abiraterone, enzalutamide, darolutamide, apalutamide).
11. [Obsolete inclusion criterion removed in Amendment 7.]
12. Documented disease progression by one or more of the following criteria:
    - PSA progression defined by a minimum of 2 elevated PSA levels with an interval of at least 1 week between the measurements. The PSA value at the screening visit should be ≥ 1 ng/ml **(For Part2/Phase 2),** ≥ 2 ng/ml (for Part 1/Phase1**)**.
    - soft tissue disease progression as defined by RECIST 1.1 criteria.
    - bone disease progression as defined by PCWG3 criteria.
13. Adequate marrow, liver and kidney function.
    - haemoglobin ≥ 10 g/dl (in absence of blood transfusion within 7 days of value obtained)
    - absolute neutrophil count (ANC) ≥ 1500/µl (1.5 x 10^9/l)
    - platelet count ≥ 100 000/µl (100 x 10^9/l)
    - aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x upper limit of normal (ULN) (≤ 5.0 x ULN if liver metastases present)
    - total bilirubin ≤ 1.5 x ULN (< 3 ULN if Gilbert's syndrome)
    - albumin ≥ 3.0 g/dl
    - creatinine clearance ≥ 60 ml/min using serum creatinine
14. Resolution of acute toxic effects of prior therapy or surgical procedures to NCI CTCAE Grade ≤ 1 (except alopecia and grade 2 peripheral neuropathy).
15. Able to swallow study treatment, to follow study instructions and to comply with study requirements.
16. Sexually active patients must agree to use condoms and an additional effective contraception during the study and for 3 months after the end of ODM-208 treatment.
17. [Obsolete inclusion criterion removed in Amendment 12.]~~**For Part 2/Phase 2 only (added in Amendment 7):** Patients with identified activating mutation in the LBD of AR in plasma ctDNA confirmed by the central testing.~~

4.3 Exclusion criteria

Subjects will be excluded from this study if they meet any of the following criteria:

1. History of pituitary dysfunction.
2. **For Part 1/Phase 1:** Known brain metastases or active leptomeningeal disease.

   For Part 2/Phase 2: Known brain metastases.
3. Other concurrent malignancies, except adequately treated basal cell or squamous cell carcinoma of the skin. Patients who have undergone potentially curative therapy for a prior malignancy are eligible provided there is no evidence of disease for > 3 years **(Part 2/Phase 2)** or ≥ 5 years **(Part 1/Phase 1)** and patient is deemed to be at low risk for recurrence.
4. Active or uncontrolled autoimmune disease requiring concurrent corticosteroid therapy.
5. Active infection or other medical condition that would make corticosteroid contraindicated.
6. Use of aldosterone antagonist (e.g. spironolactone, eplerenone) and phenytoin within 4 weeks prior start of the study treatment.
7. Patients on an unstable dose of thyroid hormone therapy within 6 months prior to the start of the study treatment.
8. Prior radiotherapy, chemotherapy within the last 4 weeks (2 weeks for oral or weekly chemotherapy; 6 weeks for nitrosoureas and mitomycin C) prior to the start of the study treatment. Concurrent radiotherapy for palliation is allowed.
9. **Part 1/Phase 1**: Use of enzalutamide within 4 weeks and abiraterone acetate within 2 weeks prior to the start of study treatment. Use of other anticancer therapy (excluding GnRH) within 4 weeks prior to the start of the study treatment. Use of immune checkpoint inhibitor within 12 weeks prior to the start of the study treatment (Amendment 4).

   Part 2/Phase 2: Use of enzalutamide and apalutamide within 3 weeks, use of darolutamide and abiraterone acetate within 2 weeks prior to the start of study treatment. Use of other anticancer therapy (excluding GnRH) within 4 weeks prior to the start of the study treatment. Use of immune checkpoint inhibitor within 12 weeks prior to the start of the study treatment.
10. **For Part 1/Phase 1 only:** Known gastrointestinal (GI) disease or GI procedure that may interfere with absorption of study treatment.
11. Poorly controlled diabetes mellitus.
12. Hypotension: systolic BP < 110 mmHg, or uncontrolled hypertension: systolic BP ≥ 160 mmHg or diastolic BP ≥ 90 mmHg (for **Part 2/Phase 2:** 95 mmHg), in 2 out of 3 recordings with optimised antihypertensive therapy.
13. Clinically significant abnormal serum potassium or sodium level.
14. Active or unstable cardio/cerebro-vascular disease, including thromboembolic events. Examples include recent (within 6 months) myocardial infarction, coronary artery bypass graft or symptomatic cerebrovascular accident or congestive heart failure (New York Heart Association class II-IV (for **Part 1/Phase 1**), III-IV (for **Part 2/Phase 2**).

15. History or family history of long QTc syndrome. Repeatable prolongation (2 out of 3 recordings) of QTcF interval > 450 ms (for **Part 1/Phase 1**), > 470 ms (for **Part 2/Phase 2**), or any clinically significant abnormality in the centrally-read ECG.
16. Major surgery within 4 weeks before the start of the study treatment.
17. Severe or uncontrolled concurrent medical condition or psychiatric illness.
18. Serious persistent infection within 2 weeks prior to the start of the study treatment.
19. **Part 1/Phase 1 (Finland, France and UK) and Part 2/Phase 2 (France and UK):** Known history of human immunodeficiency virus (HIV), or acute or chronic hepatitis B or hepatitis C disease.
    Part 2/Phase 2 (US and Finland): Patients with HIV on established antiretroviral therapy (ART) less than four weeks and/or an HIV viral load more than 400 copies/mL prior to enrolment (added in Amendment 8).
20. Known hypersensitivity to study treatment or any of its ingredients.
21. Participation in another interventional clinical trial with an investigational agent or any concurrent treatment with any investigational drug 4 weeks (immune checkpoint inhibitors 12 weeks) prior to the start of the study treatment.
22. Systemic use of the following medications within 2 weeks prior to the start of study treatment (added in Amendment 8):
    - Strong CYP3A4 inducers: E.g. avasimibe, carbamazepine, lumacaftor, phenobarbital, rifampicin, rifapentine, St John's Wort
    - P-gp inhibitors: erythromycin, clarithromycin, rifampicin, ketoconazole, itraconazole, posaconazole, artesunate-pyronaridine, ritonavir, indinavir, nelfinavir, atazanavir, glecaprevir-pibrentasvir, simeprevir, ledipasvir-sofosbuvir, verapamil, diltiazem, dronedarone, propafenone, quinidine, cyclosporine, valspodar, milk thistle (Silybum marianum)

4.4 Information collected on pre-screening and screening failures

For patients pre-screened but not included in the study, the following CRFs will be completed: pre-screening sample date and pre-screening IC date and AR LBD mutation status.

For patients screened but not enrolled in the study, the following CRFs will be completed: date of the screening visit, IC, demography (birth year and race), criteria causing the exclusion and decision of entry. In addition, all information (including concomitant treatments and medical history) about AEs related to study assessments and serious adverse events (SAEs) must be collected.

4.5 Removal of patients from treatment

Study subjects are free to discontinue the study at any time without providing a reason. However, the investigator should try to identify the reason and document it in the CRF.

In general, patient must discontinue the treatment, if the investigator or the sponsor considers the discontinuation to be medically necessary or in the best interest of the patient.

A patient must discontinue the study treatment if any of the following reasons applies:

- An AE(s) that the investigator assesses to be intolerable to the patient and related to study treatment or other toxicity that prevents further administration of study treatment as judged by the investigator. For Part 1/Phase 1 only: See section 3.3.4 for discontinuation criteria in case of a DLT.
- Disease progression as judged by the investigator (after disease progression the treatment may be continued if it is considered clinically beneficial to the patient, as judged by the investigator)
- Sponsor's major safety concern regarding the patient.
- Patient's personal decision to discontinue from the study.
- Withdrawal of consent
- Lost to follow-up.
- Protocol deviation that could affect the outcome of the study, as judged by the investigator.
- If dosing of ODM-208 is interrupted for more than 14 days.
- Sponsor terminates the study; see section 10.4.

Criteria for dosing interruption and modifications are described in section 3.3.5.

Irrespective of the reason for discontinuation, the patient should be invited to end-of-study (EOS) assessments as soon as possible. As long as the patient consents, all relevant assessments, at least those of safety, should be performed, preferably according to the schedule for the EOS assessments.

After discontinuation of ODM-208, administration of substitution treatment with glucocorticoid and fludrocortisone must be continued (see section 3.3.6.1).

The study monitor should be notified about premature discontinuations by email/phone within 24 h in the event of discontinuation due to an SAE (see section 6.5.1.3) or within 7 days in the event of discontinuation due to another reason.

The sponsor will decide if patients who prematurely discontinue will be replaced. Discontinued patients are not allowed to re-enter the study.

5. STUDY TREATMENTS

Manufacturing, packaging, and labelling of the study treatments will comply with good manufacturing practice (GMP) regulations (Annex 13 of EU guide to GMP).

5.1 Investigational medicinal product

Active ingredient	ODM-208
Pharmaceutical form:	Tablet
Unit strength:	1 mg, 5 mg, 25 mg and 50 mg
Posology:	Twice or once daily
Storage conditions	ODM-208 5 mg, 25 mg and 50 mg tablets should be stored below 30°C in a well closed container. ODM-208 1 mg tablets should be stored at 2-8ºC in a refrigerator in a well closed container.
Route of administration:	Oral administration
Duration of treatment	As long as ODM-208 considered beneficial to the patient (as judged by the investigator), or until death, intolerable toxicity or any other discontinuation criterion is met.

5.2 Auxiliary medicinal products (AMPs)

Active ingredient	Dexamethasone
Pharmaceutical form:	Tablet
Source:	Commercial
Unit strength:	0.5 mg and 1 mg
Posology:	Once daily
Route of administration:	Oral administration
Duration of treatment	Until discontinuation of ODM-208, after which dexamethasone dose is gradually decreased, see section 3.3.6.1

If 0.5 mg tablets are not available, the 1 mg dexamethasone tablet is scored and can be broken in half to give two 0.5 mg dose units.

Active ingredient	Fludrocortisone
Pharmaceutical form:	Tablet
Source:	Commercial
Unit strength:	50 µg or 100 µg
Posology:	Once daily
Route of administration:	Oral administration
Duration of treatment	Until discontinuation of ODM-208, after which fludrocortisone dose is gradually decreased, see section 3.3.6.1

Active ingredient	Hydrocortisone
Pharmaceutical form:	Tablet
Source:	Commercial
Unit strength:	10 mg
Posology:	Part 1: Three times daily Part 2: Included in the emergency kit
Route of administration:	Oral administration
Duration of treatment	Until discontinuation of ODM-208, after which hydrocortisone dose is gradually decreased, see section 3.3.6.1.

Active ingredient	Part 1: Prednisone
Pharmaceutical form:	Tablet
Source:	Commercial
Unit strength:	5 mg
Posology:	Twice daily
Route of administration:	Oral administration
Duration of treatment	Until discontinuation of ODM-208, after which prednisone dose is gradually decreased, see section 3.3.6.1.

Active ingredient	Part 1: Prednisolone
Pharmaceutical form:	Tablet
Source:	Commercial
Unit strength:	5 mg
Posology:	Twice daily
Route of administration:	Oral administration
Duration of treatment	Until discontinuation of ODM-208, after which prednisolone dose is gradually decreased, see section 3.3.6.1.

Active ingredient	Part 2: Hydrocortisone (emergency kit)
Pharmaceutical form:	Powder and solution, for solution for injection
Source:	Act-o-Vial, commercial
Unit strength:	100 mg
Posology:	Emergency case
Route of administration:	According to provider's instructions
Duration of treatment	Until end of adrenal follow-up period

5.3 Dosing

5.3.1 Selection and timing of doses

The ODM-208 tablets should be swallowed whole. The patients will be given diaries for recording the time of study treatments taken at home. In case the patient forgets to take the ODM-208 the dose should be taken as soon as possible up to 4 h after the planned dosing time. After this, the missed dose should not be taken but instead the next scheduled dose should be taken at the planned time and recorded in the diary.

5.3.1.1 Part 1/Phase 1

5.3.1.1.1 ODM-208 with dexamethasone and fludrocortisone as replacement therapy

A starting total daily oral dose is 100 mg of ODM-208 (50 mg twice daily) in Cohort 1 in Part 1A Group 1. In the morning of Day 1 (Visit 1), a single dose of ODM-208 is given with a glass of water within 30 min after meal (Part 1A) concomitantly with a minimum of oral dexamethasone 1 mg, and fludrocortisone 50 µg once daily, followed by (after 24 h) twice daily repeated dosing of ODM-208 (in the morning and the evening with 12-h dosing interval) and dexamethasone, and fludrocortisone once daily in the morning.

5.3.1.1.2 ODM-208 with hydrocortisone and fludrocortisone as replacement therapy (added in Amendment 3)

A starting total daily oral dose is 100 mg of ODM-208 (50 mg twice daily) in Cohort 1 in Part 1A Group 2 with a minimum starting dose of 40 mg of hydrocortisone divided into 3 daily doses. In the morning of Day 1 (Visit 1), a single dose of ODM-208 is given with a glass of water within 30 min after meal concomitantly with oral hydrocortisone and fludrocortisone 50 µg. The 2nd oral hydrocortisone dose will be taken in the afternoon at lunch and the 3rd oral hydrocortisone dose in the evening no later than 4-6 h before bedtime. 24 hours after the single dose of ODM-208, repeated twice daily dosing of ODM-208 with hydrocortisone three times daily, and fludrocortisone once daily will be started.

5.3.1.1.3 ODM-208 with corticosteroid replacement therapy in Part 1B (added in Amendment 4)

In the morning of Day 1 (Visit 1), a single dose of ODM-208 is given with a glass of water within 30 min after meal concomitantly with an oral glucocorticoid (dexamethasone once daily or prednisone/prednisolone twice daily or hydrocortisone three times daily) and fludrocortisone 50 µg once daily.

In 24 hours after the single dose of ODM-208, repeated daily dosing of ODM-208 will be started with corticosteroids.

Note: In case the patient forgets to take any of the corticosteroid doses, it should be taken as soon as possible.

5.3.1.1.4 ODM-208 dose selection

The dose level for Cohort 2 and all further cohorts in Part 1A will be decided by the SMB after a minimum of 3 patients have provided evaluable data on the previous dose level. The maximum allowed incremental increase can be 100% of the dose in the previous cohort in absence of

toxicity. Patients who do not experience any DLT within 24 h of the first dose will continue with repeated administration of the same dose for at least 12 weeks. Dosing of the second patient in each cohort in this part can start only after the first patient in the cohort has completed 14 days of repeated dosing and safety data from the first patient is evaluated. Dosing of subsequent patients in the same cohort can start from at least 24 h after the dosing of previous patient (see section 3.1.1).

The highest achieved individual exposure level (AUC_{0-24} 36 500 h*ng/ml) in 28-day toxicology study in dog is considered the initial maximum clinical exposure level of ODM-208 which should not be exceeded in phase I dose escalation. The number of cohorts is dependent on clinical exposure levels of ODM-208.

The dose level(s) of ODM-208 and replacement therapy and the dosing schedule(s) in Part 1B will be decided based on data from Part 1A. The dose selected for Part 1B will not exceed the highest tolerated dose given in Part 1A.

The dose and the dosing schedule in Part 2 of the study will be decided based on the data collected in Part 1. The dose selected will not exceed the highest dose administered in Part 1.

If deemed necessary to achieve better absorption, antitumour activity, and depending on the observed PK, PD and safety, the SMB can decide to modify the conditions for dosing schedule (e.g. dosing without food).

5.3.1.2 Part 2/Phase 2

In Part 2 ODM-208 is taken orally at 5 mg twice daily (total daily dose 10 mg) with a glass of water within 30 min after meal concomitantly with once daily oral dexamethasone 1.5 mg (recommended starting dose) and fludrocortisone 100 µg (starting dose) in the morning, with the possibility to titrate the dexamethasone and fludrocortisone doses if necessary. In case 5 mg twice daily is not tolerated by a subject the dose may be reduced (for example by reducing dose frequency).

5.4 Method of assigning study subjects to treatment groups

The patients will enter the study in the order they are found to be eligible. They will receive their patient numbers in the order they enter pre-screening.

5.5 Blinding

This is an open-label study.

5.6 Emergency procedures

5.6.1 Treatment of emergencies

Emergencies will be treated according to the decision of the physician in charge or the investigator, when available.

At the event of an acute adrenal crisis or if patient deteriorates while using increased doses of glucocorticoid therapy, the patient must be admitted to a hospital and parenteral corticosteroid

treatment and rehydration should be started. The initial work-up should consist of imaging and blood tests including common tests for infections, blood glucose, complete blood cell count, C-reactive protein (CRP), creatinine, creatine kinase (CK), sodium, potassium, cortisol, ACTH, TSH, free T4, phosphate, and calcium and, other tests considered necessary. This diagnostic work-up should not overly delay the start of the treatment for acute adrenal insufficiency.

Acute adrenal crisis is managed according to the institutional hospital emergency room guidelines which should not deviate from the published consensus guidelines (Arlt W et al., 2016). The guidelines recommend that the management starts with a rapid 1000 ml intravenous (i.v.) isotonic saline rehydration and a bolus of hydrocortisone 100 mg i.v. This is followed by hydrocortisone given either 200 mg as a 24h i.v. infusion or alternatively, 50 mg q.i.d. Further intravenous rehydration should be administered as required and usually the patients need 4-6 litres of rehydration during the initial 24h. Tapering of the i.v. hydrocortisone dosing may start the following day by reducing the dose of hydrocortisone to 50 mg b.i.d. When hydrocortisone is given at the dose of 50 mg/day or greater, fludrocortisone administration may be on hold. ODM-208 should be on hold until the patient's condition has been stabilised and the i.v. hydrocortisone dose is less than 50 mg/day (Arlt W et al., 2016).

Tapering of i.v. hydrocortisone dose and reinstituting to an oral regimen can be started after clinical recovery. During the following days after the parenteral hydrocortisone has been stopped the patient is at a risk of reoccurring glucocorticoid insufficiency and therefore all patients should be followed up carefully. If there was an identifiable factor causing abnormal stress, the same glucocorticoid dose as was used previously can be used also after recovery. If the crisis was deemed to be a result of inadequate basal glucocorticoid supplementation and no identified stress factor was present, the glucocorticoid supplementation dose may be increased, or the glucocorticoid may be switched to another glucocorticoid at the discretion of the investigator after discussions with the Sponsor.

Patients and their family members must be instructed to promptly inform the emergency department and other medical personnel about the study treatment-related adrenal insufficiency and the need for constant glucocorticoid and mineralocorticoid replacement therapy. Additional doses of corticosteroid and steroid emergency card for treatment-related adrenal insufficiency will be provided for patients.

Management of adrenal insufficiency is presented in Appendix 2A and Measures to prevent adrenal crisis in Appendix 2B.

5.7 Prior and other concomitant treatments

All prior lines of therapy for prostate cancer (e.g. primary therapy, hormonal therapy, type of radiation therapy and surgery) must be recorded on the CRFs.

All other concomitant treatments (including blood transfusion) taken during the study from the date of signing the IC until the EOS visit must be recorded on the CRFs for concomitant treatments. Additionally, any unplanned diagnostic, therapeutic or surgical procedure performed during the study must be recorded on the CRFs.

5.7.1 Mandatory treatment during the study

Patients who have not undergone bilateral orchiectomy and are receiving GnRH therapy prior to the study must continue the GnRH therapy during the study.

5.7.1.1 Recommended treatments during the study

Since both castration therapy and glucocorticoid replacement treatment are associated with an increased risk of bone loss especially during long-term use, bone loss preventing therapy is highly recommended for all patients. All patients should use oral calcium and vitamin D supplementation during the study. If needed according to the judgment of investigator, prophylaxis for opportunistic infections such as pneumocystis pneumonia (PCP) is recommended (Added in Amendment 4).

For Part 1 only: For patients treated with a higher glucocorticoid dose than the equivalent of 40 mg of hydrocortisone, proton-pump inhibitor (PPI) therapy (e.g. pantoprazole) is recommended.

5.7.2 Permitted treatments during the study

Any treatments that are considered necessary for the patient's welfare and which will not interfere with the study treatment, with the exceptions listed in Table 1, may be used at the discretion of the investigator.

Granulocyte colony stimulating factor (G-CSF) and other haematopoietic growth factors may be used when clinically indicated. Palliative radiotherapy is allowed during the study.

Topical steroids and inhalation steroids are permitted.

If the permissibility of a specific treatment is questionable, the investigator must consult the medical monitor.

5.7.3 Prohibited treatments during the study

Systemic use of strong CYP3A4 inducers, P-gp inhibitors and aldosterone agonists is not allowed concomitantly with ODM-208. Prohibited treatments are listed in Table 1.

Table 1. Prohibited systemic treatments during the study

Prohibited concomitant medication	Comments
Aldosterone antagonist	E.g. spironolactone, eplerenone, canrenone, potassium canrenoate
Other investigational agents	
Any treatment affecting GI motility significantly as judged by the investigator (Part 1 only)	E.g. cisapride
Antacids	From 2 h before dosing until 4 h after dosing during days when PK samples are collected.
Strong CYP3A4 inducers, e.g.: • avasimibe, carbamazepine, lumacaftor, phenobarbital, phenytoin, rifampicin, rifapentine, St John's Wort	
P-gp inhibitors: • erythromycin, clarithromycin, rifampicin • ketoconazole, itraconazole, posaconazole • artesunate-pyronaridine • ritonavir, indinavir, nelfinavir, atazanavir • glecaprevir-pibrentasvir, simeprevir, ledipasvir-sofosbuvir • verapamil, diltiazem • dronedarone, propafenone, quinidine • cyclosporine, valspodar, milk thistle (Silybum marianum)	Listed P-gp inhibitors may lead to increased ODM-208 plasma concentrations. These medications have been shown to change AUC > 200% for some co-medications. Data obtained from the University of Washington Drug Interaction Database (DIDB).

5.7.4 Precautions

The preliminary studies using human recombinant CYP enzymes suggest CYP3A4 participates in the oxidative metabolism of ODM-208. Dexamethasone, hydrocortisone, prednisone and fludrocortisone are also mainly metabolised by CYP3A4. In addition, the preliminary studies have indicated that ODM-208 is a P-gp substrate. Thus, drug-drug interactions with CYP3A4 inhibitors, CYP3A4 inducers and P-gp inhibitors may occur. The use of strong CYP3A4 inducers and P-gp inhibitors is prohibited during the study (Table 1). Use of strong CYP3A4 inhibitors should be avoided if possible. Based on in vitro metabolic clearance data the effect of the CYP3A4 inhibitors on the exposure of ODM-208 is expected to be mild.

US and Finland only: A special precaution should be used when patients receiving HIV medication (antiretroviral therapy) are enrolled due to possible drug-drug interactions with ODM-208 and dexamethasone.

Fluid volume of patients may change due to changes in mineralocorticoid status, and therefore diuretics and beta-blockers should be used with caution (see Appendix 2C).

5.8 Restrictions

Consumption of grapefruit or grapefruit juice, and use of liquorice should be avoided from the screening visit until the EOS visit.

5.9 Treatment compliance and exposure

Treatment compliance of ODM-208 will be assessed at each visit by study treatment accountability and diary. Patients are requested to return all study treatment packages (unused study treatments and empty packages) at every visit.

Any treatment deviation must be recorded. The patient should be asked about the reason for non-compliance.

Drug accountability records will be kept. The investigator must maintain accurate records demonstrating the date and amount of study treatments received, to whom and by whom dispensed (drug dispensing list) and accounts of study treatments accidentally or deliberately destroyed.

At the end of the study, any remaining study treatments will be collected and returned to the sponsor. Any discrepancies between the returned and expected returned study treatments should be explained.

5.10 Availability of ODM-208 after termination of study

There is no option to continue ODM-208 treatment therapy once the patient has discontinued the study. Subsequent treatments of the patient will be at the discretion of the attending physician.

6. STUDY PROCEDURES AND ASSESSMENTS

6.1 Study procedures

6.1.1 Part 1/Phase 1

Table 2 lists all Part 1 study procedures and indicates with an ‘x’ during which visit a particular procedure is performed.

Assessments during Visit 1 and Visit 2 are presented in Table 4 and Table 5.

Table 2. **Part 1/Phase 1:** Schedule of study events

Visit	Pre-screening	Screening	1[1]	2[2]	3	4	5	6	7	8	9	10	11	12	13, 14 etc.	Post-treatment visits	EOS	Follow-up[3]
Day		-21 to -1	1, 2, 3	8	15	22	29	43	57	71	85	113	141	169	253, 337 etc.	+7, +14, +21	+28	
Window (days)				± 2							± 4					± 2	± 4	
Week				1	2	3	4	6	8	10	12	16	20	24	36, 48 etc.			
AR mutation pre-screening IC and blood sample[15]	x																	
Informed consent		x																
Eligibility criteria and decision of entry		x																
ODM-208 administration[4]			x															
Glucocorticoid administration[4]			x															x
Fludrocortisone administration[4]			x[5]															x
Telephone contacts between visits (inquiry of symptoms)				x[6]														
Demography, height and medical history		x																
Physical examination and body temperature		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Orthostatic test[4]		x[7]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Supine BP (during PK days)			x[7]	x														x
HR		x[7]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
12-lead ECG		x[7]	x[7]	x	x	x	x	x	x	x	x	x	x	x	x		x	
ECOG performance status		x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Safety laboratory assessments (blood and urine)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[8]	x	x[8]
Blood sample for cortisol, aldosterone			x	x			x				x			x	x	x	x	x
Blood sample for renin			x	x	x		x		x		x	x	x	x	x		x	x
Blood sample for TSH, FT4		x	x						x				x		x			
Blood sample for LH, FSH			x	x			x				x							
Blood for HBA1c (for patients with diabetes)		x									x			x	x		x	

Visit	Pre-screening	Screening	1[1]	2[2]	3	4	5	6	7	8	9	10	11	12	13, 14 etc.	Post-treatment visits	EOS	Follow-up[3]
Day		-21 to -1	1, 2, 3	8	15	22	29	43	57	71	85	113	141	169	253, 337 etc.	+7, +14, +21	+28	
Window (days)				± 2							± 4					± 2	± 4	
Week				1	2	3	4	6	8	10	12	16	20	24	36, 48 etc.			
Blood samples for PK			x	x			x				x							
Blood samples (aliquots of PK samples) and urine collection for metabolite screening[9]			x	x			x				x							
Blood sample for PSA		x	x				x		x		x	x	x	x	x		x	
Blood sample for ACTH			x	x			x		x		x			x	x		x	x
Blood sample for testosterone		x	x	x			x				x			x	x			
Blood samples for PD assessments[10]			x				x				x						x[11]	x[11]
Blood sample for plasma protein binding				x														
Blood sample 1 for explorative ctDNA analyses			x														x	
Blood sample 2 for explorative ctDNA analyses			x						x			x		x	x		x	
Blood sample for germline DNA and PG[12]			x															
Radionuclide bone scan		x[13]							x[14]			x[14]		x[14]	x[14]			
Chest, abdomen and pelvic CT or MRI		x[13]							x			x		x	x			
Dispense ODM-208 and replacement treatment			x				x		x		x	x	x	x	x			
Dispense emergency card and hydrocortisone emergency kit			x															
Return study treatment							x		x		x	x	x	x	x		x	
Dispense/return diary card			x	x	x	x	x	x	x	x	x	x	x	x	x		x	
AEs, concomitant treatments and current medical conditions		x																

[1] See Table 4 for details of Part 1 Visit 1
[2] See Table 5 for details of Part 1 Visit 2
[3] Depending on time needed to taper down glucocorticoid and mineralocorticoid treatment
[4] After meal
[5] Started on Day 1

[6] Telephone calls on Day 5, 12, 19 and 26 (± 1)
[7] 3 registrations 1-2 min apart
[8] Only electrolytes
[9] Urine to be collected on visit 1 and 2 only.
[10] Androstenedione, dehydroepiandrosterone sulfate (DHEA-S), pregnenolone, 11β-hydroxyandrostenedione (11OHA4), 11-ketotestosterone (11KT)
[11] Pregnenolone and DHEA-S only
[12] The sample is used for PG assessment only if patient has signed PG IC
[13] Previous scans can be used as the baseline assessment if they were performed within 4 weeks prior to the start of the study treatment.
[14] Performed within 1 week before the actual visit (results must be available at the visit).
[15] The sample is taken only if patient has signed pre-screening IC.

6.1.2 Part 2/Phase 2

Table 3 lists all Part 2 study procedures and indicates with an ‘x’ during which visit a particular procedure is performed.

Table 3. **Part 2/Phase 2:** Schedule of study events

Visit	Pre-screening	Screening	1	2	3	4	5	6	7	8	9	10	11	12	13, 14 etc.	Post-treatment visit	EOS	Follow-up[1]	Sur-vival [17]
Day		-21 to -1	1	8	15	22	29	43	57	71	85	113	141	169	253, 337 etc.	+14	+28		
Window (days)				± 2							± 4					± 2	± 4		±14
Week				1	2	3	4	6	8	10	12	16	20	24	36, 48 etc.				Every 12 wks
AR mutation pre-screening IC and blood sample	x																		
Informed consent		x																	
Eligibility criteria and decision of entry		x																	
ODM-208 administration[2]			x																
Glucocorticoid administration			x															x	
Fludrocortisone administration			x															x	
Telephone contacts between visits (inquiry of symptoms)				x[3]															
Demography, height and medical history		x																	
Physical examination and body temperature		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[15]	x	x[15]	
Weight		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		
Supine BP and HR		x[4]	x[4]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
12-lead ECG		x[4]	x[4]	x	x	x	x	x	x	x	x	x	x	x	x		x		
ECOG performance status		x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Safety laboratory assessments (blood and urine)[10]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[5]	x	x[5]	
Blood sample for cortisol, aldosterone[11]			x	x			x				x					x	x	x	
Blood sample for ACTH[11]			x	x			x				x						x	x	
Blood samples for dexamethasone, fludrocortisone and CBG[11]			x	x	x	x	x	x	x	x	x								
Blood sample for renin[11]			x	x	x		x		x		x			x	x		x		
Blood sample for TSH[12]		x	x								x			x[6]					

Visit	Pre-screening	Screening	1	2	3	4	5	6	7	8	9	10	11	12	13, 14 etc.	Post-treatment visit	EOS	Follow-up[1]	Sur-vival [17]
Day		-21 to -1	1	8	15	22	29	43	57	71	85	113	141	169	253, 337 etc.	+14	+28		
Window (days)				± 2							± 4					± 2	± 4		±14
Week				1	2	3	4	6	8	10	12	16	20	24	36, 48 etc.				Every 12 wks
Blood for HBA1c (for patients with diabetes)[10]		x									x			x	x		x		
Blood samples for PK			x[16]	x[13]					x[14]										
Blood sample for PSA[12]		x	x		x		x		x		x	x	x	x	x		x		
Blood sample for testosterone/other steroids[12]		x	x	x			x				x			x	x				
Blood samples for androstenedione, DHEA-S, pregnenolone/other steroids[11]			x	x			x				x						x[7]	x[7]	
Blood sample 1 for explorative ctDNA analyses			x														x		
Blood sample 2 for explorative ctDNA analyses			x						x			x		x	x		x		
Blood sample for CTC count[11]			x								x								
Blood sample for AR-V7 on CTC[11]			x																
Blood sample for explorative plasma			x		x	x	x												
Blood sample for germline DNA and PG			x																
Radionuclide bone scan		x[8]							x[9]			x[9]		x[9]	x[9]				
Chest, abdomen and pelvic CT or MRI		x[8]							x[9]			x[9]		x[9]	x[9]				
Dispense ODM-208 and replacement treatment			x				x		x		x	x	x	x	x				
Dispense emergency card and hydrocortisone emergency kit			x																
Return study treatment							x		x		x	x	x	x	x		x		
Dispense/return diary card			x	x	x	x	x	x	x	x	x	x	x	x	x		x		
~~Digital symptom questionnaire (voluntary)[18]~~		~~x~~	~~x[17]~~																
AEs, concomitant treatments and current medical conditions		x																	

Visit	Pre-screening	Screening	1	2	3	4	5	6	7	8	9	10	11	12	13, 14 etc.	Post-treatment visit	EOS	Follow-up[1]	Sur-vival [17]
Day		-21 to -1	1	8	15	22	29	43	57	71	85	113	141	169	253, 337 etc.	+14	+28		
Window (days)				± 2							± 4					± 2	± 4		±14
Week				1	2	3	4	6	8	10	12	16	20	24	36, 48 etc.				Every 12 wks
Survival status		x																	x

[1] Depending on time needed to taper down glucocorticoid and mineralocorticoid treatment.
[2] After meal
[3] Telephone calls on Day 5, 12, 19, 26, 36 (week 5) and 50 (week 7) (± 1)
[4] 3 registrations 1-2 min apart
[5] Only electrolytes
[6] Every 3 months until 6 months, thereafter every 6 months
[7] Pregnenolone and DHEA-S
[8] Previous scans can be used as the baseline assessment if they were performed within 4 weeks prior to the start of the study treatment
[9] Performed within 1 week before the actual visit (results must be available at the visit)
[10] Local laboratory analysis
[11] Central laboratory analysis
[12] For TSH, PSA and testosterone, screening samples are analysed at the local laboratory, whereas the samples from Visit 1 onwards are analysed at the central laboratory
[13] In day 8, PK samples will be taken predose and 2 h after dose
[14] In day 57, PK samples will be taken predose
[15] Physical examination only
[16] For sampling time points, see Table 6
[17] ~~Patients will fill in the questionnaire using a digital application at screening (querying the past 7 days) and at home between visits every third day during the first 3 months, and after that once a week until week 24.~~
[18] ~~Digital symptom questionnaire will not be used in France.~~
[19] Follow up every 12 weeks at visits or telephone calls with the subject, current physician or local death registries; added in Amendment 12.

6.1.3 Procedures during the pre-screening period

A potential study subject will receive both written and verbal information about the pre-screening, and will have an opportunity to ask questions and sufficient time to decide whether to participate in the AR mutation pre-screening test (optional in Part 1, mandatory in Part 2). Mutations in the LBD of AR in plasma ctDNA will be analysed centrally.

- A signed and dated written AR mutation pre-screening IC will be obtained.
- Blood samples for AR analysis will be taken.
- When results are available, the subject will be contacted to inform him about the results and discuss with him the subsequent steps.

6.1.4 Procedures during the screening period - Day -21 to Day 1

A screening visit will take place within 21 days before the first ODM-208 administration at Visit 1 (Day 1). If the subject has an ongoing glucocorticoid replacement treatment, it is important to continue the daily glucocorticoid intake during the whole screening period and to switch it to study replacement therapy on Day 1. A prospective study subject will receive both written and verbal information about the study, and will have an opportunity to ask questions and sufficient time to decide whether to participate in the study. A signed and dated written IC(s) will be obtained.

The following procedures will be performed at the screening visit to ensure that all the inclusion/exclusion criteria are met:

- Demographic data will be recorded.
- Physical examination, body temperature, weight and height will be recorded.
- Medical history will be recorded.
- Orthostatic test (Part 1 only) see section 6.5.4.1), BP, heart rate (HR) and 12-lead ECG will be recorded. ECG, BP and HR will be recorded after 10 min rest in supine position (3 consecutive registrations 1-2 min apart).
- ECOG performance status will be assessed.
- A blood sample for safety laboratory assessments (haematology and clinical chemistry), including TSH (Part 1: and fT4) and urine sample for urinalysis will be collected. Blood sample for glycated hemoglobin (HBA1c) for patients with diabetes will be collected.
- A blood sample for determination of local PSA concentration will be collected (previous PSA value can be used as the baseline assessment if it was taken within 4 weeks prior to the start of the study treatment).
- A blood sample for local testosterone assessment will be collected.
- Radionuclide bone scan will be done and documented (prior bone scan can be used as the baseline assessment if it was performed within 4 weeks prior to the start of the study treatment).

- Chest, abdomen and pelvic CT or MRI will be done and documented (previous CT or MRI scans can be used as the baseline assessment if they were performed within 4 weeks prior to the start of the study treatment).
- Part 2 only: A non-mandatory symptom questionnaire will be introduced and instructed to the subject, and filled in by the subject. ~~The symptom questionnaire will not be used in France.~~ Applicable only to initial 40 patient cohort in Part 2/Phase 2 (excluding France).
- AEs, concomitant treatments (see section 5.7) and current medical conditions will be inquired.

6.1.5 Procedures during the treatment period

6.1.5.1 Part 1/Phase 1: Visits 1 and 2

6.1.5.1.1 Part 1: Visit 1 - Day 1, Day 2, and Day 3

The patients will arrive at the study centre in the previous evening, or alternatively in the morning of Day 1 after overnight fast (at least 8 h). Patients are allowed to leave the study centre after all procedures on Day 3 have been performed.

Part 1A Group 1

On Day 1, after pre-dose procedures have been performed (Table 4), breakfast will be served, and the first dose of study treatment and a minimum of dexamethasone 1 mg and fludrocortisone 50 µg will be taken. After study treatment administration, blood samples and urine will be collected and supine BP, HR, orthostatic test and 12-lead ECG will be recorded at timings presented in Table 4. The patients will not receive an evening dose of ODM-208 on Day 1.

On Day 2, after pre-dose procedures have been performed (Table 4), breakfast will be served, and second dose of study treatment and dexamethasone 1 mg and fludrocortisone 50 µg will be taken. Starting from the morning of Day 2, the patients will take ODM-208 twice daily, and dexamethasone 1 mg and fludrocortisone 50 µg once daily. Blood samples and urine will be collected, and supine BP, HR, orthostatic test and 12-lead ECG will be performed at timings presented in Table 4.

Part 1A Group 2 (added in Amendment 3)

See section 1.2.2.3 and Appendix 3 for hydrocortisone dose selection.

On Day 1, after the pre-dose procedures have been performed (Table 4), a breakfast will be served, and the first dose of study treatment and hydrocortisone and fludrocortisone 50 µg will be taken. After study treatment administration, blood samples and urine will be collected and a supine BP, HR, orthostatic test and a 12-lead ECG will be recorded at timings presented in Table 4. The 2nd oral hydrocortisone dose will be taken at lunch and the 3rd hydrocortisone dose no later than 4-6 h before bedtime. The patients will not receive an evening dose of ODM-208 on Day 1.

On Day 2, after the pre-dose procedures have been performed (Table 4), a breakfast will be served, and the 2nd dose of study treatment and hydrocortisone and fludrocortisone will be taken.

Starting from the morning of Day 2, the patients will take ODM-208 twice daily, fludrocortisone once daily and hydrocortisone 3 times a day. Blood samples and urine will be collected, and a supine BP, HR, orthostatic test and a 12-lead ECG will be performed at the timings presented in Table 4.

After all study assessments on Day 3 have been performed and morning dose of ODM-208 and glucocorticoid, and fludrocortisone doses have been taken, study treatment containers, diary and steroid emergency card and emergency kit will be given to the patient. The patient has to be educated regarding continuous need for corticosteroid replacement treatment and the need for glucocorticoid dose adjustment during acute illness or other stress situations (see section 3.3.5.2). Thereafter, the patient will be allowed to leave the study centre. The patient will continue taking the ODM-208 twice daily with the replacement therapy at home until Visit 2.

Part 1B (Added in Amendment 4)

The procedures on Day 1 – Day 3 are as in Part 1A (see above). ODM-208 will be dosed with a glucocorticoid (dexamethasone or prednisone/prednisolone or hydrocortisone) and fludrocortisone. For cohorts with high starting dose of glucocorticoid and fludrocortisone see Appendix 3.

Table 4. Study procedures at Visit 1 in Part 1A and B

Procedure	Day 1										Day 2			Day 3
	Pre-dose	0h	0.5 h	1.0 h	1.5 h	2 h	4 h	6 h	9 h	12 h	24 h	26 h	36 h	48 h
Physical examination and body temperature	x													x[5]
Weight	x													
Supine BP	x[1]					x		x	x	x	x[3]		x[3]	
Orthostatic test[4]						x								x[5]
HR	x[1]					x		x	x	x	x[3]	x	x[3]	x[5]
12-lead ECG	x[1]					x	x	x		x	x[3]	x	x[3]	x[5]
ECOG performance status	x													
Safety laboratory assessments (blood and urine)	x													
Blood sample for electrolytes (Na and K)											x[3]			x[3]
Blood sample for renin	x													
Blood sample for TSH, FT4	x													
Blood sample for LH, FSH	x													
Blood sample for PK and metabolite screening	x		x	x	x	x	x	x	x	x	x[3]			
Urine collection for metabolite screening[2]	x	x									x			
Blood sample for PSA	x													
Blood sample for ACTH, aldosterone, cortisol	x													
Blood sample for testosterone	x			x		x		x		x	x[3]		x[3]	
Blood sample for PD assessments[6]	x													

Procedure	Day 1										Day 2			Day 3
	Pre-dose	0h	0.5 h	1.0 h	1.5 h	2 h	4 h	6 h	9 h	12 h	24 h	26 h	36 h	48 h
Blood sample 1 and 2 for explorative ctDNA plasma analysis	x													
Blood sample for germline DNA and PG	x													
ODM-208 administration[4]		x									x		x[8]	x
Dexamethasone administration, if applicable[4]		x									x			x
Hydrocortisone administration, if applicable		x	x[7]								x	x[7]		x
Prednisone/Prednisolone administration, if applicable		x								x	x		x	x
Fludrocortisone administration[4]		x									x			x
Dispense ODM-208, glucocorticoid and fludrocortisone														x
Dispense diary, emergency card and emergency kit														x
AEs, concomitant treatments and current medical conditions	x													

[1] 3 registrations 1-2 min apart
[2] Total urine collected in 2 batches, between 0-12 h and 12-24 h
[3] Before study treatment administration
[4] After meal
[5] After study treatment administration
[6]Androstenedione, dehydroepiandrosterone sulfate (DHEA-S), pregnenolone, 11β-hydroxyandrostenedione (11OHA4), 11-ketotestosterone (11KT)
[7] 2nd dose after lunch and 3rd dose the latest 4–6 h before bedtime
[8] If twice daily dosing

Timings of PK sampling, HR, BP and 12-lead ECG recordings may be changed after evaluation of Cohort 1 data, if considered necessary by the SMB. The total number of HR, BP and ECG assessments may also be changed.

6.1.5.1.2 Part 1: Visit 2 - Day 8 (± 2)

Patients will arrive at study centre in the morning of Visit 2 in Part 1 fasted and without taking ODM-208 on that morning. Glucocorticoid and fludrocortisone will be taken at home at awakening. ODM-208, will be administered at the study centre after pre-dose procedures have been performed and breakfast served. After study treatment administration, blood samples and urine will be taken, orthostatic test, supine BP, HR, 12-lead ECG will be recorded, and ODM-208 and glucocorticoid will be administered at timings presented in Table 5.

Thereafter, patient will be allowed to leave the study centre. Patient will continue taking the ODM-208 daily, fludrocortisone once daily and glucocorticoid once/twice/three times a day (depending on type of the glucocorticoid treatment) at home until Visit 3.

Table 5. Study procedures at Visit 2 in Part 1A and B

Procedure		Day 8									
	At awakening	**Pre-dose**	**0**	**0.5 h**	**1h**	**2h**	**3h**	**4h**	**6h**	**9h**	**12h**
Physical examination and body temperature		x									
Weight		x									
Supine BP		x							x		x[1]
Orthostatic test[4]							x				
HR		x					x		x		x[1]
12-lead ECG		x					x		x		x[1]
ECOG performance status		x									
Safety laboratory assessments (blood, urine)		x									
Blood sample for aldosterone, ACTH, cortisol		x									
Blood sample for renin		x									
Blood sample for LH, FSH		x									
Blood sample for PK and metabolite screening		x		x	x	x	x	x	x	x	x[3]
Urine collection for metabolite screening[2]		x									
Blood sample for testosterone		x									x[3]
Blood sample for plasma protein binding						x			x		
ODM-208 administration[4]			x								x[6]
Dexamethasone administration, if applicable[4]	x										
Hydrocortisone administration, if applicable	x			x[5]							
Prednisone/Prednisolone administration, if applicable	x										x
Fludrocortisone administration[4]	x										
Dispense/return diary card											x
AEs, concomitant treatments and current medical conditions	x										

[1] After study treatment administration
[2] Total urine collected between 0-12 h
[3] Before study treatment administration
[4] After meal
[5] 2nd dose after lunch and 3rd dose the latest 4–6 h before bedtime
[6] If twice daily dosing

6.1.5.1.3 Part 1: Visit 3 - Day 15 (± 2) and subsequent visits (± 2 days until week 10 and ±4 days thereafter)

Patients will arrive at study centre in the morning of the visit fasted and without taking ODM-208 on that morning. Glucocorticoid and fludrocortisone will be taken at home at awakening. After pre-dose procedures have been performed, breakfast will be served and ODM-208 will be

administered. All procedures are done once during each visit. Procedures at Visit 3 and subsequent visits are presented in Table 2. Patients are allowed to leave the study centre after all procedures have been performed.

Patient will continue taking the ODM-208 daily, fludrocortisone once daily and glucocorticoid once/twice/three time a day (depending on the glucocorticoid treatment) at home, until subsequent visit.

6.1.5.2 Part 2/Phase 2: Visits 1 and 2

6.1.5.2.1 Part 2: Visit 1 - Day 1

In Part 2, the patients will arrive at the study centre in the previous evening, or alternatively in the morning of Day 1 after overnight fast (at least 8 h). ODM-208, glucocorticoid and fludrocortisone will be administered at the study centre after pre-dose procedures have been performed and breakfast (non-standardised) served. Study procedures performed during Visit 1 in Part 2 are presented in Table 6. Patients will stay at the study centre for 12 h and are allowed to leave the study centre after all procedures on Day 1 have been performed, and second daily dose of ODM-208 has been taken.

Patient will continue taking the ODM-208 twice daily and glucocorticoid and fludrocortisone once daily at home until Visit 2.

Table 6. Study procedures at Visit 1 in Part 2/Phase 2

Procedure	Day 1						
	Pre-dose	0 h	0.5h	2 h	6 h	10 h	12 h
Physical examination and body temperature	x						x[3]
Weight	x						
Supine BP	x[1]			x	x		x[3]
HR	x[1]			x	x		x[3]
12-lead ECG	x[1]			x	x		x[3]
ECOG performance status	x						
Safety laboratory assessments (blood and urine)	x						
Blood sample for renin	x						
Blood sample for TSH,	x						
Blood sample for PSA	x						
Blood sample(s) for ACTH, aldosterone, cortisol	x						
Blood samples for dexamethasone, fludrocortisone, CBG	x						
Blood sample for testosterone/other steroids	x						
Blood sample for androstenedione, DHEA-S, pregnenolone /other steroids	x						
Blood sample 1 and 2 for explorative ctDNA plasma analysis	x						
Blood sample for CTC count	x						

Procedure	Day 1						
	Pre-dose	0 h	0.5h	2 h	6 h	10 h	12 h
Blood sample for AR-V7 on CTC	x						
Blood sample for explorative plasma analyses	x						
Blood sample for germline DNA and PG	x						
Blood sample for PK			x	x	x	x	
ODM-208 administration[2]		x					x
Dexamethasone administration[2]		x					
Fludrocortisone administration[2]		x					
Dispense ODM-208, glucocorticoid and fludrocortisone							x
Dispense diary, emergency card and hydrocortisone emergency kit							x
AE inquiry, concomitant treatments and current medical conditions	x						

[1] 3 registrations 1-2 min apart
[2] After meal
[3] After study treatment administration

6.1.5.2.2 Part 2: Visit 2 - Day 8 (± 2)

Patients will arrive at study centre in the morning of the Visit 2 in Part 2 fasted and without taking ODM-208 on that morning. Glucocorticoid and fludrocortisone will be taken at home at awakening. After pre-dose procedures (i.e. all procedures apart from the 2-h post-dose ODM-208 PK blood sample) have been performed, breakfast will be served and ODM-208 will be administered. 2 hours after dosing ODM-208, a blood sample will be taken for PK measurements. Procedures at Visit 2 in Part 2 are presented in Table 3. Patients are allowed to leave the study centre after all procedures on Day 8 have been performed.

Patient will continue taking the ODM-208 twice daily and glucocorticoid and fludrocortisone once daily at home until Visit 3.

6.1.5.2.3 Part 2: Visit 3 – Day 15 ((± 2) and subsequent visits (± 2 days until week 10 and ±4 days thereafter)

Patients will arrive at study centre in the morning of the visit fasted. Glucocorticoid and fludrocortisone will be taken at home at awakening. All procedures at Visit 3 are to be performed before the dosing of ODM-208. After the procedures have been performed, breakfast will be served and ODM-208 will be administered. All procedures are done once during each visit. Procedures at Visit 3 and subsequent visits are presented in Table 3. Patients are allowed to leave the study centre after all procedures have been performed.

Patient will continue taking the ODM-208 twice daily and glucocorticoid and fludrocortisone once daily at home, until subsequent visit.

6.1.5.2.4 Telephone calls

Telephone calls will be done on Day 5, 12, 19, 26 (± 1) (both Part 1 and Part 2) and Day 36 and 50 (± 1) (weeks 5 and 7; Part 2 only) to inquire the patient's general status and symptoms related to adrenal insufficiency.

6.1.6 Procedures during the post-treatment period

6.1.6.1 Post-treatment visits

6.1.6.1.1 Part 1: Post-treatment visits – 7, 14, 21 (±2) days (added in Amendment 3)

Adrenal recovery of the patients will be followed at the post-treatment visits, performed at 7, 14, and 21 (±2) days after the last dose of ODM-208.

The following laboratory tests will be taken in the morning:

- Cortisol
- Aldosterone
- Electrolytes (Sodium [Na], Potassium [K])

The following procedures will be performed:

- Physical examination will be carried out, and body temperature and weight will be measured
- HR will be measured and orthostatic test will be done

Replacement therapy will be continued according to the instructions provided in section 3.3.6.1.

6.1.6.1.2 Part 2: Post-treatment visit – 14 (±2) days

Adrenal recovery of the patients will be followed at the post-treatment visit, performed at 14 (±2) days after the last dose of ODM-208.

The following laboratory tests will be taken in the morning:

- Cortisol
- Aldosterone
- Electrolytes (Sodium [Na], Potassium [K])

The following procedures will be performed:

- Physical examination will be carried out
- Blood pressure and pulse rate will be measured

Replacement therapy will be continued according to the instructions provided in section 3.3.6.1.

6.1.6.2 Part 1/Phase 1 and Part 2/Phase 2: End-of-study (EOS) visit

Patients will have an EOS visit 28 (+/-4) days after the last dose of ODM-208 treatment. The following procedures will be performed at the EOS visit:

- Physical examination, body temperature, and weight

- BP, HR and 12-lead ECG
- Orthostatic test (Part 1 only)
- Safety laboratory assessments: haematology, chemistry and urinalysis. Blood for HBA1c for patients with diabetes. ~~Blood samples for dexamethasone and fludrocortisone analysis.~~
- Determination of PSA concentration
- Exploratory ctDNA analyses
- Pregnenolone and DHEA-S determinations
- Drug accountability
- AEs, concomitant treatments and current medical conditions
- Return diary card

Corticosteroid substitution will be continued according to the instructions in section 3.3.6.1.

6.1.6.3 Part 1/Phase 1 and Part 2/Phase 2: Adrenal recovery follow-up (Added in Amendment 3)

If a patient still needs glucocorticoid and/or mineralocorticoid therapy at the EOS visit, adrenal recovery of the patient will be followed by a visit at 4 weeks and, if needed, at 8 weeks. In the event that replacement therapy needs to be used beyond 8 weeks after EOS, the investigator or study nurse should contact the patient at 16 weeks and, if needed, at 24 weeks from the EOS, and record the use of replacement therapy and its dose. See Table 7 below for details.

Table 7. Procedures at adrenal recovery follow-up

Procedure/Data collected	**Follow-up visits**		**Follow-up contact**
	Visit 4 weeks (±4 days) after EOS	**Visit 8 weeks (±4 days) after EOS**	**Call 16 and 24 weeks (±4 days) after EOS**
Physical examination, weight[1], body temperature[1], blood pressure and pulse rate	x	x	
Blood tests for cortisol, aldosterone and electrolytes (Na, K), renin[1]	x	x	
Serum pregnenolone and DHEA-S	x	x	
If clinically indicated orthostatic test and blood test for ACTH	x	x	
Recording of glucocorticoid and mineralocorticoid use (dose and product name)	x	x	x
AEs related to ODM-208	x		

[1] Part 1 only.

6.1.6.4 Part 2/Phase 2 only: Survival follow-up (added in Amendment 12)

Each patient will be followed for survival starting from the last study visit or possible adrenal recovery follow-up call. This will be performed by telephone, e-mail, chart review, or review of public records, in compliance with local practices and regulations. Patients who discontinue study treatment will move into survival follow-up and will be contacted at least every 12 weeks to assess for survival status until death, loss to follow up, or withdrawal of consent, whichever occurs first. Where possible, cause of death and further treatments for prostate cancer since the last follow-up will be recorded.

The sponsor may request updated survival status during the study before final analysis. Survival follow may continue for up to 2 years after the EOS visit for the last patient.

Investigators should attempt to also follow up and acquire survival status for subjects whose EOS visit precedes Amendment 12 coming into effect. For such patients the investigator should use available means to establish patient status before approaching the patient for further survival follow-up (for which patients will be asked to provide additional informed consent).

6.2 Efficacy assessments

6.2.1 Assessment of antitumour effects

6.2.1.1 Prostate specific antigen (PSA)

Serum total PSA concentration will be determined centrally at Day 1, Week 2 (Part 2/Phase 2 only), Week 4 and after that every 4 weeks until 24 weeks and every 12 weeks thereafter (see section 6.1 for timings). In case of PSA progression, a confirmatory test should be obtained 3-4 weeks later.

6.2.1.2 Soft tissue response

Chest, abdomen and pelvic CT or MRI will be performed at screening, and then every 8 weeks until week 24 and every 12 weeks thereafter (see section 6.1 for timings). Same imaging modality (CT or MRI) per patient should be used throughout the study. Objective response rate (ORR) of soft tissue (visceral or nodal disease) will be assessed by RECIST 1.1.

6.2.1.3 Bone

Radionuclide bone scan will be performed at screening, and then every 8 weeks until week 24 and every 12 weeks thereafter (see section 6.1 for timings).

6.2.1.4 ECOG performance status and clinical progression

ECOG performance status will be assessed at every visit during ODM-208 treatment (see section 6.1).

Clinical progression will be assessed. See 3.3.7 for details in definition of clinical progression.

6.2.1.5 Part 2/Phase 2 only: Circulating tumour cell (CTC) response (added in Amendment 7)

Blood sample for CTC enumeration will be taken at Day 1 and Week 12. CTC enumeration will be performed using CellSearch® system (Menarini Silicon Biosystems). CTC response is defined as CTC count nonzero at baseline and 0 at week 12.

6.2.1.6 Part 2/Phase 2 only: Survival status (added in Amendment 12)

Survival status for each subject should be obtained by site personnel approximately every 12 weeks after the subject's last study visit or possible adrenal recovery follow-up call.

6.3 Pharmacokinetic assessments

6.3.1 Blood and urine sampling

Before the start of the study, instructions for the collecting, handling, storage and transportation of blood and urine samples will be provided in a laboratory manual to the study centres.

Bioanalytical details and criteria for acceptance of the results will be described in bioanalytical plan and reported in bioanalytical report.

6.3.2 Blood samples for pharmacokinetics

6.3.2.1 Part 1/Phase 1

Blood samples (2 ml of K2-EDTA blood) for the determination of ODM-208 in plasma are collected on Day 1 and Day 8. The timepoints are presented in Table 4 and Table 5, respectively.

For blood sampling, a forearm vein can be cannulated on Day 1 and Day 8 until 12 h sampling. The exact time of sampling and the most recent study treatment administration will be recorded on the CRF. If a deviation from the scheduled sampling time is longer than the accepted time range, the reason for the deviation should be recorded on the corresponding CRF. The accepted time ranges are available in 'Time windows for PK blood samples' document. Timings of blood sampling may be modified, if considered necessary by the SMB, after analysing available PK results.

On Day 29 (Visit 5) and at Week 12 (Visit 9) the blood samples will be collected before the study treatment administration (0 h).

6.3.2.2 Part 2/Phase 2

The PK blood samples for the determination of ODM-208 in plasma will be collected on day 1, 8 and 57. On day 1 PK samples will be taken 0.5, 2, 6 and 10 h after dosing. On day 8 PK samples will be taken predose and 2 h after dosing and on day 57 predose as outlined in Section 6.1.2, Table 3 and Table 6.

On the PK sample collection day, accurate information on dosing and timing of the 2 doses of study treatment on the day prior to PK collection day and on the day of PK sampling will be recorded.

Instruction on sample collection, handling, labelling, storage and shipment will be provided in the laboratory manual.

6.3.3 Part 1/Phase 1 only: Blood sampling for plasma protein binding

A 6 ml blood sample for determination of the binding of ODM-208 to plasma proteins will be taken 2 h and 6 h after the study treatment administration on Day 8 of Part 1.

6.3.4 Part 1/Phase 1 only: Metabolite screening

Plasma samples collected in Part 1 at the PK sampling points on Days 1 and 8 (see section 6.1), and on Day 29 (Visit 5) and at Week 12 (Visit 9) may also be used for metabolite screening and for determination of plasma concentrations of metabolites. PK spare samples can be used for metabolite screening, if feasible.

6.3.5 Part 1/Phase 1 only: Urine samples for metabolite screening

Urine samples for metabolite screening will be collected in Part 1. Pre-dose sample will be collected on Day 1, and total urine will be collected on Day 1 between 0-12 h and 12-24 h (2 batches), and on Day 8 between 0-12 h.

6.3.6 Determination of ODM-208 concentration

The concentration of ODM-208 in plasma of PK samples will be determined with a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

6.3.7 Determination of ODM-208 binding to plasma proteins

Binding of ODM-208 to plasma proteins will be determined using an appropriate technique.

6.3.8 Calculation of pharmacokinetic (PK) variables (Part 1/Phase 1)

PK variables will be calculated from the ODM-208 concentrations measured in plasma after study treatment administration on Day 1 and Day 8. The PK parameters will be calculated by non-compartmental method using validated Phoenix WinNonlin® (Pharsight Corporation, a Certara Company) software by the sponsor. The actual time of sampling will be used in the calculation of PK parameters. Possible outlying concentrations excluded from the PK analysis will be reported and exclusion justified in the study report.

The following PK parameters will be calculated from the concentration-time data of ODM-208 after single dose administration on Day 1:

C_{max} The maximum observed concentration of concentration-time curve

t_{max} The time to reach the maximum observed concentration

AUC_t The area under the concentration-time curve from time zero to the last sample with the quantifiable concentration calculated with linear trapezoidal rule

AUC_∞ The area under the concentration-time curve from time zero to infinity, AUC_∞ will be determined by adding AUC_t to the extrapolated area that will be determined dividing the last quantifiable concentration by λz.

λ_z The terminal elimination rate constant from log-linear portion of a concentration-time curve

V_z/F Apparent volume of distribution during elimination phase.

Cl/F Apparent clearance following oral administration.

$t_{½}$ The terminal elimination half-life that will be calculated with the equation ln2/λz

The following PK parameters for ODM-208 will be calculated after repeated dosing on Day 8:

C_{max} The maximum observed concentration of concentration-time curve

t_{max} The time to reach the maximum observed concentration

AUC_t The area under the concentration-time curve from time zero to the last sample with the quantifiable concentration calculated with linear trapezoidal rule

AUC_∞ The area under the concentration-time curve from time zero to infinity, AUC_∞ will be determined by adding AUC_t to the extrapolated area that will be determined dividing the last quantifiable concentration by λz.

λ_z The terminal elimination rate constant from log-linear portion of a concentration-time curve

V_z/F Apparent volume of distribution during elimination phase.

Cl/F Apparent clearance following oral administration.

$t_{½}$ The terminal elimination half-life that will be calculated with the equation ln2/λz

C_{av} The average concentration in plasma after repeated administration calculated as $AUC_{0\text{-}12h}$ divided by the dosing interval 12 h for twice daily dosing

At least C_{max}, t_{max} and AUC_t will be calculated online for evaluation by the SMB. If actual time of the sampling is not available, the planned sampling time will be used in the online calculations.

Pre-dose concentrations (C_0) of ODM-208 on Day 29 and Week 12 will be reported.

6.3.9 Assessment of metabolite screening (Part 1/Phase 1)

Metabolite profiles in plasma and urine will be characterised by using liquid chromatography-mass spectrometry (LC-MS). In addition, plasma concentrations for selected metabolites can be determined in connection to these analyses, if needed. These assessments will be performed without claiming compliance with good clinical practice (GCP) but aligned with the recommendations given in the EMA Reflection Paper (EMA/INS/GCP/532137/2010). Issues

and criteria concerning the metabolite screening results will be described and reported in a separate report.

6.4 Biomarkers

6.4.1 Pharmacodynamic assessments

6.4.1.1 Part 1/Phase 1

Testosterone and other steroid assessments will be performed to study PD effects of ODM-208. See section 6.1 for timing of blood sampling.

Other steroids that may be assessed if analytically feasible are e.g.

- Androstenedione
- Dehydroepiandrosterone sulfate (DHEA-S)
- Pregnenolone
- 11-ketotestosterone (11KT)
- 11β-hydroxyandrostenedione (11OHA4)

6.4.1.2 Part 2/Phase 2

Steroid (e.g. ~~T~~testosterone, androstenedione, DHEA-S and pregnenolone) assessments will be done to study PD effects of ODM-208. See section 6.1 for timing of blood sampling.

The concentration of steroids will be determined with validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods.

6.4.2 Explorative biomarker assessments

6.4.2.1 Prospective AR mutation testing in plasma ctDNA

6.4.2.1.1 Part 1/Phase 1

Blood may be collected during pre-screening period for central plasma ctDNA assessment to analyse point mutations in the LBD of the AR by digital polymerase chain reaction (dPCR) to select mutation positive patients. (Added in Amendment 6).

6.4.2.1.2 Part 2/Phase 2

Blood will be collected during pre-screening period for central plasma ctDNA assessment using the next-generation sequencing test Guardant360 (https://guardant360.com/wp-content/uploads/2020/05/gene-list.png) covering a total of 74 cancer genes relevant to multiple solid tumours including point mutations in the LBD of the AR gene to define the AR mutation status of the patients ~~select AR mutation positive patients~~ (Added in Amendment 7).

6.4.2.2 Part 2/Phase 2: Splice variant AR-V7 in circulating tumour cells

Blood will be collected on Day 1 for AR splice variant AR-V7 analysis in CTC samples (Epic Sciences) (Added in Amendment 7).

6.4.2.3 Additional explorative plasma assessments

The timepoints for blood collection for exploratory plasma assessments (including ctDNA) are presented in section 6.1.

In addition, unused plasma or serum samples taken originally for the steroid analytics or analysis of ODM-208 and its metabolite screening may be used for exploratory research purposes related to the response to study treatment.

The samples will be stored in the sponsor's sample repository to allow possible exploratory analyses related to the absorption, distribution, metabolism, excretion, clinical response and resistance, pharmacodynamics and safety of study treatment and its metabolites. Such explorative analyses would aim to identify circulating factors such as nucleic acids, proteins and biochemical metabolites. Plasma biomarker results will be reported as separate reports, if appropriate.

Instructions for collection, handling, storage and transportation of samples will be provided before the start of the study.

6.4.3 Germline DNA and pharmacogenomics

A blood sample for DNA extraction will be taken at Visit 1. Possible analyses of the extracted DNA sample for two purposes include:

- germline DNA reference when analysing genomic tumour material from e.g. biopsy or circulating tumour DNA.
- PG assessment (in phase 1, optional and done only if the patient has signed the PG IC; mandatory in phase 2).

The germline DNA and PG assessments will be done as an exploratory research.

The aim of the PG research is to assess if genetic polymorphisms relate to the absorption, distribution, metabolism, excretion, clinical response and resistance mechanisms, pharmacodynamics and safety of study treatment, its metabolites or other drug treatments given in this study.

Instructions for the collection, handling, storage and transportation of samples will be provided before the start of the study. Germline DNA and PG analyses will be reported as separate reports as appropriate. DNA will be stored in the sponsor's sample repository.

6.5 Safety assessments

6.5.1 Adverse events

6.5.1.1 Definitions

An AE is any untoward medical occurrence in a study subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal

product, whether or not related to the investigational medicinal product. The definition also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

Thus, an AE may be an appearance or worsening of any undesirable sign or symptom, any worsening of the current medical conditions or onset of a new disease, compared with the previous observations or a clinically significant adverse change in a laboratory variable or other diagnostic finding (e.g. ECG).

Disease progression, per se, should not be reported as an AE. If there are separate identifiable clinical signs and symptoms that result from the disease progression (for example bone pain), the clinical signs and symptoms are to be reported as an AE.

An SAE is any untoward medical occurrences that at any dose

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect, or
- is an important medical event jeopardizing the patient or requiring intervention to prevent serious outcome (examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; development of drug dependency or drug abuse; overdose or interaction).

In this study, the following events will not be reported as SAEs:

- hospitalisation and elective surgery for treatment of pre-existing condition that has not exacerbated during the study
- planned hospitalisation to simplify procedure or treatments
- Disease progression, per se, should not be recorded as an SAE. If disease progression leads to clinical signs and symptoms that meet the criteria of seriousness, these events and not the disease progression itself should be reported as a SAE. In this case, disease progression should be mentioned on the SAE form as the likely cause for the event in the "Alternative Explanation" section.

Other significant AEs are marked haematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that lead to an intervention including

- withdrawal of the investigational product
- reduction of its dose
- significant additional concomitant therapy

6.5.1.2 Assessment of adverse events

All AEs must be elicited, documented and reported by the investigator to the sponsor from the time that a study subject signs the IC form until the EOS visit i.e. 28 (+/− 4) days after the last dose of study treatment. In addition, any AEs that occur after the EOS visit during the adrenal recovery period up to 24 weeks, and which are considered to be related to ODM-208 treatment or to a study procedure have to be reported.

The AE safety follow-up should continue until the EOS visit, death of the patient, or discontinuation.

If the patient is not able to attend the EOS visit, the safety follow-up period is still considered to be 28 days and all AEs informed to the investigator during this period should be reported.

SAEs and other significant AEs should be followed up until resolved or until the event is considered a chronic or stable outcome, or both.

AE may be notified to the investigator by the study subject or observed by the investigator clinically, or be an adverse change in laboratory assessment results. The investigator will evaluate the subject's AEs at each visit by asking a standard question such as "Since you were last asked, have you felt unwell or different from the usual in any way?".

The investigator will assess and record the causality and severity of the AEs. Causality should be assessed in relation to ODM-208 with corticosteroid replacement therapy (see criteria for causality and severity below).

Causality criteria:

Related: The temporal relationship of the AE/SAE onset to the administration of ODM-208 with replacement therapy makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the AE/SAE.

Not related: The temporal relationship of the AE/SAE onset to the administration of ODM-208 with the replacement therapy makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

Severity criteria:

All AEs will be graded according to the NCI CTCAE version 4.03:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Severity is included in this grading and there is no separate severity assessment.

In case a patient experiences an AE that is not presented in NCI CTCAE, the severity will be assessed according to following criteria:

Grade 1 = Mild AE, discomfort noticed, but it does not affect normal activity

Grade 2 = Moderate AE, discomfort sufficient to reduce or affect normal daily activity

Grade 3 = Severe AE, incapacitating with inability to work or perform normal daily activity; or hospitalisation or prolongation of hospitalisation indicated

Grade 4 = Life-threatening AE

Grade 5 = Death (fatal AE)

From the time that a study subject candidate signs the IC form, newly appearing diagnosed diseases will be recorded on the AE CRF.

From screening to the EOS visit investigators must report all AEs to the sponsor on a specific AE CRF irrespective of their assessment of the causal relationship of the investigational medicinal product to the event.

6.5.1.3 Reporting of serious adverse events by the investigator

The investigator must report all SAEs within 24 h of becoming aware of an SAE. SAEs must be reported within 24 h regardless of the time that may have elapsed since the time the event occurred and regardless of the causal relationship of investigational medicinal product to the event.

All SAEs should be reported electronically by the investigator or other relevant study centre personnel and submitted by the investigator. Optionally, if the investigator is not able to submit the SAE electronically, the paper version of the SAE form can be completed and sent by e-mail or faxed to drugsafety@orionpharma.com or +358 10 426 3739. The SAE reporting contact information can be found on the SAE form and in the investigator's study file.

If the initial report is reported by phone or e-mail to the study monitor or other contract research organisation (CRO) personnel and the study centre personnel are unable to fill in the SAE electronically within 24 h, a paper SAE form will be initiated by the person receiving the report. The investigator must report the SAE electronically as soon as possible.

The minimum criteria for SAE reporting are: the event or outcome meets the SAE definition, the event happens to an identifiable study subject, and the event is reported by an identifiable and qualified reporter (usually an investigator or other qualified study centre personnel)

A follow-up report to an SAE should be prepared if any relevant change in the condition of the study subject occurs after the initial report. The follow-up report should be documented as an update to the initial report.

SAEs that occur after the EOS visit on Day 28 (+/− 4 days) after the last study treatment administration should be reported, if the investigator feels that there is a reasonable possibility for the event to be related to ODM-208 treatment or to a study procedure.

6.5.1.4 Reporting of serious adverse events to competent authorities and ethics committees

The sponsor is responsible for expediting all suspected unexpected serious adverse reactions (SUSARs) as well as other safety issues requiring expedited reporting to the relevant authorities within applicable timelines. ~~In some countries, t~~This task may be performed by the ~~CRO, as~~ delegate of the responsible sponsor.

Notification of the ethics committees (ECs) and institutional review boards (IRBs) about all relevant events (SUSARs, other relevant safety information) will be performed by the sponsor or CRO as a delegate of the responsible sponsor and/or by the investigator according to applicable regulations.

The expectedness evaluation is required for regulatory reporting and it is performed by the sponsor or delegate of the responsible sponsor. The expectedness in this study is evaluated against the Reference safety information section in the current ODM-208 Investigator's Brochure.

6.5.2 Special situations

The special situations with study treatment are defined as: medication error, overdose, abuse, misuse and interaction.

These special situations with study treatment are reported on the Special situations with study treatment CRF even if there is no accompanying AE. All clinical manifestations in relation to these special situations will be reported as AEs or SAEs at the same time using the corresponding section of the CRF.

6.5.3 Pregnancy during the study

Whenever it becomes known that a partner of a study subject became pregnant or was pregnant during exposure to study treatments, the outcome of the pregnancy, delivery, postpartum recovery and the clinical condition of the offspring during the neonatal period should be reported, subject to the partner's consent. A pregnancy follow-up form will be provided to the investigator for completion after the sponsor or delegate of the responsible sponsor has received the initial report.

Any case of pregnancy during a clinical study should be reported by the investigator in the same way as an SAE.

6.5.4 Clinical safety assessments

Safety will be assessed by AEs, laboratory tests, physical examination, vital signs including orthostatic test and 12-lead ECG.

6.5.4.1 Part 1/Phase 1 only: Orthostatic test

Orthostatic test will be performed after a meal. HR and systolic and diastolic BP will be measured in a supine position after 10 min at rest (see section 6.1 for timings). 3 recordings will be performed 1-2 min apart at screening.

After the last supine measurement, the patient is asked to stand up. HR and BP will be measured after the patient has been standing 1 and 3 min.

Orthostatic test is assessed as abnormal, if there is a drop in systolic BP of ≥ 20 mmHg, or in diastolic BP of ≥ 10 mmHg.

Control assessments can be performed according to the judgement of the investigator.

6.5.4.2 Heart rate and blood pressure

HR, systolic and diastolic BP will be measured in a supine position after 10 min at rest (see section 6.1 for timings). 3 recordings will be performed 1-2 min apart before dosing on Day 1. Single recordings will be performed at other timepoints after dosing.

6.5.4.3 12-lead ECG

A 12-lead ECG will be recorded in a supine position after 10 min at rest (see section 6.1 for timings). On PK sampling days, recordings should be started 5 min before PK sampling. 3 recordings will be performed 1-2 min apart at screening and before dosing on Day 1. Single recordings will be performed at other time points. ECG recordings should be completed before starting blood sampling.

6.5.4.4 Physical examination

A standard physical examination including recording the weight will be performed by the investigator (see section 6.1 for timings). Height will be recorded at screening only.

6.5.4.5 Body temperature

Body temperature will be measured from mouth (oral), ear (tympanic) or skin (temporal) (see section 6.1 for timings). For each patient, the method of temperature measurement must be same (oral, tympanic or temporal) throughout the study.

6.5.4.6 Part 1/Phase 1 only: Adrenal gland size

The adrenal gland size will be measured with CT or MRI at screening, and then every 8 weeks until week 24, and every 12 weeks thereafter. The same imaging modality (either CT or MRI) will be used throughout the study. For the imaging time schedule, see section 6.1.

6.5.4.7 Part 2/Phase 2 only: Symptom questionnaire (added in Amendment 7)~~ – not applicable in France~~

Applicable only to initial 40 patient cohort in Part 2/Phase 2 (excluding France).

Digital application for symptom tracking will be offered as an option for patient on a voluntary basis. The application is Kaiku® Health ePRO, a CE-marked class I software. Patient will be asked to fill a symptom questionnaire consisting of questions related to symptoms of adrenal insufficiency and general well-being. Patient will be asked to fill questionnaire at screening (querying the past 7 days), every third day during the first 3 months, and after that once a week. The questionnaire will be filled in until Visit 12 (at 24 weeks) at maximum, or until the end of ODM-208 treatment, should the patient discontinue the treatment before 24 weeks, or whenever the patient decides not to continue filling in the questionnaire.

Patients are informed that symptom collection is intended for non-urgent situations only. In urgent situations patients must directly seek treatment from an emergency hospital. The application will notify and instruct the patient to contact the study site, if symptom reported required a more detailed assessment by the study site personnel. The application may be used for secure communication between the patient and the study site. The symptom report will be transferred to the study site.

6.5.5 Laboratory safety assessments

The visits at which the safety laboratory assessments are performed are presented in section 6.1.

In case there are clinically relevant findings, control assessments may be performed according to the judgement of the investigator.

Instructions for the collection, handling, storage and transportation of samples will be provided before the start of the study.

The following laboratory tests will be performed after at least 8 h of fasting (excluding post-treatment and follow-up visits).

6.5.5.1 Part 1/Phase 1

Haematology:
- Haemoglobin
- Haematocrit
- Erythrocyte count
- Leukocyte count
- Thrombocytes
- Differential count (lymphocytes, monocytes, eosinophils, neutrophils, basophiles)
- Mean corpuscular volume
- Mean corpuscular haemoglobin

Clinical chemistry:
- ACTH
- Albumin
- Albumin corrected calcium
- Aldosterone
- Alkaline phosphatase and bone-specific alkaline phosphatase
- ALT
- Amylase
- AST
- Bilirubin conjugated
- Bilirubin total
- Cortisol
- C-reactive protein
- Creatinine
- Creatine kinase
- Creatine kinase MB isoenzyme
- Free thyroxine (fT4)
- Follicle stimulating hormone (FSH)
- Glucose
- HBA1c (for patients with diabetes only)
- High-density lipoprotein (HDL) cholesterol
- International normalised ratio (INR) (for patients using coumarin derivative only)
- Lactate dehydrogenase
- Low-density lipoprotein (LDL) cholesterol
- Luteinising hormone (LH)
- Magnesium
- Phosphate
- Potassium
- Renin

- Sodium
- Total cholesterol
- Triglycerides
- TSH

Urinalysis by dipstick:
- Erythrocytes
- Glucose
- Leukocytes
- Protein

6.5.5.2 Part 2/Phase 2

Haematology:
- Haemoglobin
- Haematocrit
- Erythrocyte count
- Leukocyte count
- Thrombocytes
- Differential count (lymphocytes, monocytes, eosinophils, neutrophils, basophiles)
- Mean corpuscular volume
- Mean corpuscular haemoglobin

Clinical chemistry:
- ACTH
- Albumin
- Albumin corrected calcium
- Aldosterone
- Alkaline phosphatase
- ALT
- Amylase
- AST
- Bilirubin total and conjugated
- Cortisol
- Corticosteroid-binding globulin (CBG)
- C-reactive protein
- Creatinine
- Glucose
- HBA1c (for patients with diabetes only)
- High-density lipoprotein (HDL) cholesterol
- International normalised ratio (INR) (for patients using coumarin derivative only)
- Lactate dehydrogenase
- Low-density lipoprotein (LDL) cholesterol
- Phosphate
- Potassium
- Renin
- Sodium
- Total cholesterol
- Triglycerides

- TSH

Urinalysis by dipstick:
- Erythrocytes
- Glucose
- Leukocytes
- Protein

In addition, blood dexamethasone and fludrocortisone will be analysed.

6.6 Changes due to COVID-19 pandemic (added in Amendment 7)

The following arrangements should be applied in the event that the patients are not able to attend visit at the study centre as a direct result of the COVID-19 pandemic. All arrangements described in this section apply only to the extent that protocol requirements cannot be met because of COVID-19-related reasons. Study centre visits should take place to the extent possible and usual protocol requirements adopted for all subjects as soon as COVID-19 situation allows. Specific information on COVID-19-related deviations from the procedures described in the protocol will be captured in the case report form. Exceptional measures taken in response to COVID-19 and their impact on study results, such as tests done in a local laboratory, will be explained, assessed and reported in the clinical study report following ICH E3.

During the treatment period and follow-up any visit may be performed by telephone or video call (see Table 8).

Table 8. Procedures at remote visits

Time	Telephone/video visit to replace treatment period, EOS visit	Telephone/video visit to replace adrenal recovery F-U visit
Weight[1]	x	x
Heart rate and blood pressure[2]	x	x
Laboratory safety assessments[3]		
Haematology	x	x[4]
Chemistry	x	x
Urinalysis	x	
PSA	x	
Study treatment[5]		
Symptoms of corticosteroid over- or under-replacement	x	x
AEs and SAEs	x	x
Concomitant treatments	x	x

[1] The measurement is taken using the home scale

[2] Optional, if home device is available. Performed in supine position after at least 5 min rest before the morning dose of the study treatment.

[3] Standard biochemical, electrolyte and haematological test panels of the local laboratory will be accepted A copy of the laboratory report with local reference range should be provided.

[4] Sodium, potassium, aldosterone and cortisol

[5] Study treatment shipped to patient's home.

In case these assessments cannot be obtained at the specified time, the benefit:risk ratio for the patient to continue in the study should be reassessed.

7. DATA COLLECTION AND MANAGEMENT

The investigators and study centre personnel will prepare and maintain accurate source data for each study subject about clinical findings specified in the protocol. Source data include patient records, laboratory results and patient diaries. The data from source documents will be recorded into an electronic data capture (EDC) system, Medidata Rave (Medidata Inc), using eCRFs at the study centre. Externally produced data will be uploaded directly into the EDC system or transferred to the sponsor at agreed time intervals. All data on the eCRFs must be verifiable in the source data or patient records unless eCRF data are declared as source data.

Investigators and other relevant study centre personnel will be trained to use the eCRFs and other systems for data collection. After completion of training, they are provided with user names and authorised access to enter and correct data as applicable depending on the system.

Study subjects who choose to use the ePRO digital application for symptom and sign data collection will be trained to use the application. Subjects will also be provided with usernames and authorised access to enter data (the symptom questionnaire will not be used in France).

Electronic queries about missing, misleading, incomplete or illogical data will appear in the EDC system. An audit trail within the system will track all changes/corrections made. The investigator has to confirm the content of the eCRF with an electronic signature.

Individual data fields in the EDC system may be locked on an ongoing basis during the study. The fields may be unlocked if further updates are needed. When all data have been entered and all queries resolved, the whole database will be locked. Only authorised and well-documented updates to the study data are possible after the database lock.

Further details regarding data collection and management are presented in the data management plan.

8. STATISTICAL METHODS

8.1 Statistical hypotheses

No formal statistical hypotheses were formulated.

8.2 Estimation of sample size

No formal sample size calculation was performed. Separate dose escalation (3+3) will be performed in Part 1A Group 1 and Part 1A Group 2.

The purpose of the extension to the phase 2 expansion, introduced in Amendment 12, will be to achieve 2 cohorts of approximately 60 subjects per cohort under phase 2 conditions with and without AR LBD mutations to enable more accurate estimate of PSA response and rPFS, to support phase 3 study design as well as giving balance between the AR LBD mutation negative and positive patient population.

Simon's two-stage design (Simon R, 1989) was used to estimate the number of AR LBD mutation negative mCRPC patients in Part 2 extension (added in Amendment 12). The null hypothesis that the true PSA response rate is 5% will be tested against a one-sided alternative. Criteria for continuation of patient enrolment may be met at any time during the conduct of the study. However, if not met, then in the first stage, 23 subjects will be enrolled. If there are one or fewer PSA responses in these 23 subjects, the study will be stopped, otherwise, enrolment will continue as planned. The null hypothesis will be rejected if six or more PSA responses are observed in 56 patients. This design yields a significance level of 0.05 and power of 80% when the true response rate is 15%.

8.3 Analysis populations

The patients will be classified into the following data sets before database lock:

- Intention-to-treat (ITT) population: all enrolled patients, regardless of whether they are later found to be ineligible, a protocol violator, never treated or not evaluated.
- Per-protocol (PP) population: Patients who have completed the study according to the protocol without relevant major protocol deviations. A list of protocol deviations will be prepared. Classification and evaluation of the relevance of major protocol deviations will be made before database lock.
- Safety population: all patients who have received at least 1 dose of study treatment.

The analysed dataset for the primary evaluation in Part 1 will be safety population and in Part 2 primarily ITT population and secondarily PP population. Criteria for different data sets will be defined in the statistical analysis plan.

8.4 Statistical analyses

Statistical analyses are described in more detail in the statistical analysis plan.

All evaluations will be performed for observed cases only and data will be presented separately by study part (Part 1, Part 2), pooled over study parts and by dose level and by AR LBD mutation status, as~~if~~ appropriate.

Confidence intervals (CIs): A two-sided type I error rate of 0.05 together with estimated 95% CIs will be used in this study.

Missing values and outliers: Statistical analysis will be performed for observed cases only. Possible sensitivity analyses may be carried out to evaluate the robustness of the statistical results, particularly the impact of potential outliers.

Missing event occurrence dates will be imputed as the earliest possible date. Missing event dates e.g., due to withdrawal of consent, lost to follow up or not known to have died at the analysis cut-off date, will be right censored (e.g. using last assessment in the study). Detailed methods are described in the statistical analysis plan.

Data transformations: PK parameters (at least AUC and C_{max}) will be analysed after logarithmic transformation and the geometric mean will be calculated. Appropriate transformations may be used to analyse other parameters if found to improve conditions underlying the use of statistical methods.

Baseline is defined as last available measurement before study treatment starts. In case several measurements are taken at baseline, a mean value of measurements is used as a baseline.

8.4.1 Demographic and other baseline characteristics

All relevant demographic and baseline characteristics will be summarised using descriptive statistics. The number and reasons for discontinuations will be listed and tabulated by treatment groups.

An authorised person will code medical history and concomitant diseases using standard coding dictionaries.

8.4.2 Treatment compliance and extent of exposure

The number of patients exposed to ODM-208 and corticosteroid replacement treatments, and dose and the duration of exposures will be tabulated with descriptive statistics.

8.4.3 Analysis of efficacy

8.4.3.1 Analysis of antitumour effects

8.4.3.1.1 PSA

PSA data will be analysed descriptively by dose. Best response and the number of responders (30% and 50% decline from baseline) will be presented, and percentage of change from baseline will be tabulated by time point and by dose.

8.4.3.1.2 Soft tissue response

The frequency of responders according to RECIST 1.1 (Eisenhauer EA et al., 2009) of soft (target and non-target) lesions will be presented. ORR will be presented by time point. ORR is defined as best objective response of complete response (CR) or partial response (PR) by RECIST 1.1. Descriptive statistics of sum of lesion diameters and percent changes will be presented.

8.4.3.1.3 Bone

Bone progression by PCWG3 (Scher HI et al., 2016) and the changes from baseline in the number of lesions on bone scan will be reported as “no new lesions” or “new lesions”.

8.4.3.1.4 ECOG performance status

The ECOG performance status and the changes from baseline will be summarised with descriptive statistics. Time to ECOG deterioration will be measured from enrolment to deterioration of ECOG >1 point. Patients who do not experience event or die will be censored.

Time to ECOG deterioration will be summarised with descriptive statistics and Kaplan-Meier method.

8.4.3.1.5 Clinical disease progression

Clinical disease progression symptoms will be summarised.

8.4.3.1.6 Time to disease progression

Median time to PSA progression (deaths censored) by PCWG3 criteria (Scher HI et al., 2016) and median time to radiographic progression (deaths censored) by RECIST 1.1 (Eisenhauer EA et al., 2009) and PCWG3 criteria (Scher HI et al., 2016) will be summarised with descriptive statistics and Kaplan-Meier method.

8.4.3.1.7 Duration of objective response

Duration of objective response is defined as time from complete response or partial response to radiographic progression of disease, unequivocal clinical progression or death, duration of objective response will be summarised using descriptive statistics.

8.4.3.1.8 Radiographic progression-free survival (rPFS)

Radiographic progression-free survival (rPFS) is defined as time from enrollment (i.e. decision for entry) to radiographic progression or death from any cause. If patient experiences no event, the patient will be censored. rPFS will be summarised with descriptive statistics and Kaplan-Meier method.

8.4.3.1.9 Time on treatment

The time from the start of ODM-208 treatment until discontinuation of ODM-208 treatment will be summarised with descriptive statistics and Kaplan-Meier method, if appropriate.

8.4.3.1.10 Part 2/Phase 2 only: CTC response

The proportion of patients with CTC response (CTC0) will be presented. CTC responses will be tabulated using descriptive statistics. In addition, a proportion of patients achieving a decline ≥ 30% from baseline in CTC count will be tabulated.

8.4.3.1.11 Overall survival (OS)

Overall survival (OS) is defined as time from enrolment (i.e. decision for entry) to date of death from any cause. The date and cause of death will be recorded. Status of OS will be assessed until end of study. The OS distribution will be estimated using Kaplan-Meier method and Kaplan-Meier curves including median survival times and their 95% confidence intervals will be reported.

8.4.4 Pharmacokinetic analysis

The PK variables (C_{max}, t_{max}, AUC_t, AUC_∞, V_z/F, Cl/F and $t_{½}$) will be summarised separately after single and repeated dosing using descriptive statistics, and plotted with appropriate figures.

In Part 1, the dose proportionality of ODM-208 on the PK variables AUC_t and C_{max} will be analysed using a general linear regression model ('power model') for the log-transformed AUC_t and C_{max} values. The comparison of PK results of ODM-208 between single dose and repeated dose administration will be made by a linear mixed model, including sampling day as repeated factor, and dose level as a between factor.

8.4.5 Pharmacodynamic analyses

8.4.5.1 Steroid variables

The actual values and the changes from baseline for testosterone and other steroid variables will be summarised using descriptive statistics.

8.4.6 Analysis of explorative plasma assessments

The role of specific activating AR LBD mutation in antitumor activity will be examined and tabulated using descriptive statistics.

AR amplification and AR-V7 (Part 2 only) data will be tabulated using descriptive statistics, and their relationship to antitumor activity of ODM-208 will be examined. Other identified genetic alterations will be tabulated using descriptive statistics.

Explorative analyses will aim to identify circulating factors such as nucleic acids, proteins and biochemical metabolites. Plasma biomarker results may be reported in separate reports, as appropriate.

8.4.7 Population pharmacokinetic/pharmacodynamic analysis

A population PK and PK/PD model for ODM-208 is planned to be developed. Population PK and PK/PD modelling may be applied to evaluate the role of covariates and PK/PD relations in terms of safety and efficacy related endpoints. Details of the modelling and possible simulation process will be described in a separate population PK/PD modelling plan.

8.4.8 Analysis of germline DNA and pharmacogenetics

Genetic polymorphisms may be analysed in relation to significant variation or specific scientific question in PK, PD or safety variables of ODM-208. If such analysis will be performed, the results will be reported in separate reports.

8.4.9 Safety analysis

8.4.9.1 Analysis of adverse events

AEs reported during the study will be classified by system organ classes and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) coding system. The AEs as event counts and subject counts will be displayed with frequency tables. The number and proportion (%) of patients having each AE will be given.

The AEs will be graded by toxicity grade classified by NCI CTCAE version 4.03. Severity is included in this grading and there is no separate severity assessment. Incidences of AEs will also

be summarised by maximum severity. SAEs and other significant AEs will be evaluated case-by-case. Occurrence of DLTs (Part 1 only) will be summarised with descriptive statistics. AEs occurring before, after the initiation of study treatment and post treatment will be listed.

8.4.9.2 Clinical safety analysis

8.4.9.3 Vital signs

Vital signs, and orthostatic test (Part 1 only) will be summarised using descriptive statistics. The absolute values and the changes in vital signs from baseline will be shown. Abnormal orthostatic test (drop in systolic BP of ≥ 20 mmHg, or in diastolic BP of ≥ 10 mmHg) will be tabulated by time point (Part 1 only).

Orthostatic values will be tabulated according to normal, clinically not relevant abnormality and clinically relevant abnormality (Part 1 only).

8.4.9.4 12-lead ECG

The actual values and corresponding changes from baseline for ECG variables (RR, PR, QT, QRS, QTc-Bazett and QTc-Fridericia) will be summarised using descriptive statistics.

Interpretation of 12-lead ECG will be tabulated (normal, clinically not relevant abnormality and clinically relevant abnormality). The number of patients with QT or QTc-Fridericia prolongation will be tabulated. The prolongation criteria for QT and QTc-Fridericia are as follows:

- > 450 ms
- > 470 ms
- > 500 ms
- increase of 30 to 60 ms from baseline
- increase of > 60 ms from baseline

Concentration-QTc-Fridericia relationship will be examined to evaluate proarrhythmic risk. A line-scatter plot with linear regression fit for QTc-Fridericia change from baseline and ODM-208 with 1-sided 95% CI will be produced.

8.4.9.5 Laboratory safety analysis

Laboratory safety variables will be summarised using descriptive statistics. Absolute values and changes from baseline will be tabulated. The values will be also categorised into low, normal and high according to their reference ranges. Clinically significant changes from baseline will be tabulated for some specific laboratory assessments, if applicable.

8.4.9.6 Analysis of prior and concomitant treatments

Prior and concomitant treatments will be coded using the anatomical therapeutic chemical (WHODrug) classification system. Concomitant treatments during the study treatment period and at the EOS visit are tabulated separately.

8.4.9.7 Other observations related to safety

Body temperatures and changes from baseline will be listed by patient and time point.

Possible special situations with study treatment, pregnancy data, and physical examination findings will be listed. Descriptive statistics for adrenal gland size with percent changes will be presented (Part 1 only).

8.4.9.8 Analysis of the symptom questionnaire

All data received from digital symptom questionnaire will be summarised using descriptive statistics. The potential association between questionnaire symptom and signs data and other study data, e.g. adverse event, will be determined, where feasible.

8.5 Interim analyses

No formal interim analysis is planned in the study. However, in Part 1 the SMB will review the accumulating data (section 3.3.2 and the SMB charter). In Part 2, Simon's two-stage will be used for patients without AR LBD mutations. Criteria for continuation of patient enrolment may be met at any time during the conduct of the study. However, if not met, an interim analysis will be conducted after 23 patients are enrolled in the first stage and have had at least 8 weeks of follow-up, to assess the antitumor effects.

9. DATA QUALITY ASSURANCE

9.1 Training

An investigator meeting or initiation meeting will be arranged for the investigators and other relevant study centre personnel. This meeting will include a review of the protocol, CRF completion and study procedures.

The investigators will ensure that appropriate training relevant to the study is given to the medical, nursing and other personnel involved in the study. The investigators will also ensure that any information relevant to the conduct of the study is forwarded to other relevant study centre personnel.

9.2 Case report forms

Electronic queries about missing, misleading, incomplete or illogical data will appear in the EDC system. An audit trail within the system will track all changes/corrections made. The investigator has to confirm the content of the eCRF with an electronic signature.

9.3 Monitoring, audits and inspections

The study monitor will visit the study centre regularly as agreed by the investigator and the sponsor. The study monitor will ensure that the study complies with GCP and applicable regulatory requirements and that the protocol is followed in all aspects, including the randomisation procedure, accurate recording of results, reporting of AEs, drug accountability and record keeping. Furthermore, it will be verified that the clinical facilities remain appropriate,

and that the CRFs correspond with source data. Further details regarding monitoring are presented in the monitoring manual.

The study may be audited by independent representative(s) of the sponsor or inspected by the competent authorities (CAs). For these purposes, the study monitor, auditors and inspectors will be allowed direct access to hospital or patient records/source data of the study subjects, original laboratory data etc., as far as they are related to the study.

It is essential that the investigator and other relevant members of the study centre team are available during the monitoring visits, audits and inspections, and that they devote sufficient time to these processes.

9.4 Laboratories and other vendors

Details regarding laboratory measurements and ECG analyses are presented in the separate instructions. Quality certificates are required from all safety laboratories.

Bioanalytics and metabolite screening will be performed in accordance with the principles of good laboratory practises (GLP) and GCP. Bioanalytics and steroid measurements will be performed using validated methods.

10. FURTHER REQUIREMENTS AND GENERAL INFORMATION

10.1 Investigators and study administrative structure

10.1.1 Investigators

Should the investigator transfer one of his/her responsibilities to other members of the study centre team, he/she must have this documented.

In the event of changes in key study centre team members, the responsible investigator must ensure that the successor is fully informed and capable of following the procedures.

A curriculum vitae in English must be available from all investigators who sign the protocol, and from other relevant persons.

10.1.2 Safety monitoring board (SMB)

A SMB will be established for the study. The duty of the SMB is to protect the ethical and safety interests of the study subjects and all others who may possibly be exposed to study treatments.

The SMB will include principal investigators from study centres taking part in Part 1 and the external endocrinologist. The SMB support group will include representatives from the sponsor and the clinical CRO. The SMB support group members may attend the SMB meetings but do not have voting rights. The voting rights are extended to the principal investigators only.

The sponsor will provide the SMB with mutually agreed safety, pharmacokinetic and antitumour activity data.

To ensure that the safety data generated during the study are received by all study centres, the principal investigator at each centre in phase I will be a member of the SMB. All investigators, including co-investigators, will receive all SUSAR reports on an ongoing basis throughout the study. In addition, full listings of all safety data, including CIOMS reports of all SAEs, will be made available for the SMB members before each formal cohort SMB meeting.

In Part 2, investigators who participated in the SMB during Part 1 will review safety data periodically.

Further details regarding the composition and responsibility of the SMB are presented in the SMB charter and section 3.3.2.

10.2 Insurance

The sponsor will provide clinical trial liability insurance for study subjects in all participating countries according to local regulations.

10.3 Retention of records

The investigator agrees to keep the following documentation in the investigator's study file: patient records, including a subject screening log, a subject identification list, all original signed IC forms, a copy of CRFs and records of drug dispensing.

The study files at the study centres will be stored in the respective archives for 15 years, after which the sponsor will be contacted and the possibility of future archiving will be mutually agreed upon.

10.4 Completion of the study

10.4.1 Completion of the study

The end of the study is defined as the date of the last subject's last visit or last contact with the study site.

Study centres will be closed upon study completion. A study centre is considered closed when all required documents and study supplies have been collected and a study completion/termination visit has been performed.

10.4.2 Premature discontinuation of the study

The sponsor reserves the right to prematurely terminate the study for valid scientific or administrative reasons. After such a decision, the investigator must contact all participating study subjects within 7 days, and invite them for an EOS visit. At this visit, all delivered study treatments and other study materials must be collected. All CRFs must be completed up to the EOS visit.

10.5 Reports, publications and communication of results

Orion wishes to collaborate with the investigators to publish the results as timely as possible, without compromising accuracy or industrial property rights. The preparation, submission and authorship for publications containing the study results shall be in accordance with a process determined by mutual written agreement among the sponsor and participating investigators and in accordance with international criteria for authorship; see International Committee of Medical Journal Editors recommendations, available at http://www.icmje.org.

Orion remains the exclusive owner of the study data defined by the protocol.

11. ETHICS

11.1 Ethics committee

The study protocol, patient information sheets, IC forms for Part 1 and Part 2, and all other necessary documents will be submitted to an independent EC for review according to local regulations.

The investigator is responsible for obtaining a favourable opinion from the EC/IRB for the study, submitting any amendment(s), and communicating study-related safety issues as requested by the EC. The investigator should file all correspondence with the EC in the investigator's study file. Relevant copies of this correspondence should be forwarded to the sponsor.

11.2 Subject data protection

Information collected during the course of the study will be stored in a database and used in the further development of ODM-208 and thereafter for as long as the information is relevant to patient care. The use includes the transfer of data to CAs in the European Union, the United States or other countries for the purpose of obtaining and maintaining marketing authorisations. All information is handled confidentially and according to local laws and regulations.

The patients can be identified in the CRFs only by study subject number and birth year.

The confidentiality of PG data will be protected according to local laws and regulations.

Personal information used for identification on the ePRO application (symptom questionnaire; not used in France) will be protected from unauthorised access, use, or disclosure. Personal data sent from the application to the server will be encrypted in transit, and stored on computer systems that have limited access and are in controlled facilities located in EU. The patients can be identified in the data transferred to the Sponsor only by study subject number.

11.3 Ethical conduct of the study

The study will be conducted in accordance with the Declaration of Helsinki guiding physicians in biomedical research involving human subjects.

The study shall not be initiated before favourable opinion from the EC/IRB and approval from the CA has been obtained for the protocol, including its appendices.

The study will be conducted in compliance with the protocol, ICH GCP (R2) and applicable regulatory requirements. A substantial amendment shall not be implemented until the protocol amendment has received a favourable opinion from the EC and approval from the CA. Only in case of the need to eliminate an immediate hazard(s) to study subjects, the investigator may implement deviation from the protocol without prior favourable opinion from the EC and approval from the CA for the protocol amendment.

In case of serious breaches, the MHRA GCP Inspectorate must be notified according to MHRA Guidance for the notification of serious breaches of GCP or the study protocol (see http://www.mhra.gov.uk).

11.4 Patient information and informed consent

The investigator will ensure that each patient is fully informed about the objectives and procedures of the study. The investigator will also explain any possible risks with participating in the study and answer all questions regarding the study. After this, the patient will be given sufficient time to make a decision regarding participation in the study.

Patients will be informed of their right to discontinue the study at any time without their medical care or legal rights being affected. Patients will also be informed that representatives of the sponsor or CA may inspect relevant parts of their medical records and study data.

The investigator will obtain a signed and dated consent from each patient before any study related procedures are performed. A copy of each signed and dated IC will be given to the patient. The investigator should confirm the receipt of every IC by entering the date of the consent both on the CRF and also on the subject screening log and identification list.

A separate AR mutation pre-screening IC will be obtained.

Additional informed consent will be asked from subjects, whose EOS visit precedes Amendment 12 coming into effect, to allow survival follow-up.

12. REFERENCE LIST

Antonarakis ES (2015) Predicting treatment response in castration-resistant prostate cancer: could androgen receptor variant-7 hold the key? Expert review of anticancer therapy. 15 (2): 143-5.

Arlt W et al. (2016) Society for Endocrinology Endocrine Emergency Guidance: Emergency management of acute adrenal insufficiency (adrenal crisis) in adult patients. Endocr Connect. 5 (5): G1-G3.

Attard G et al. (2012) Clinical and biochemical consequences of CYP17A1 inhibition with abiraterone given with and without exogenous glucocorticoids in castrate men with advanced prostate cancer. J Clin Endocrinol Metab. 97 (2): 507-16.

Bertaglia V et al. (2017) An exploratory analysis of the association between levels of hormones implied in steroid biosynthesis and activity of abiraterone in patients with metastatic castration-resistant prostate cancer. Minerva Urol Nefrol. 69 (4): 349-358.

Bornstein SR et al. (2016) Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 101 (2): 364-89.

Boudadi K et al. (2016) Resistance to Novel Antiandrogen Therapies in Metastatic Castration-Resistant Prostate Cancer. Clin Med Insights Oncol. 10 (Suppl 1): 1-9.

Brasso K et al. (2015) Enzalutamide antitumour activity against metastatic castration-resistant prostate cancer previously treated with docetaxel and abiraterone: A multicentre analysis. Eur Urol. 68 (2): 317-24.

Charmandari E et al. (2014) Adrenal insufficiency. Lancet. 383 (9935): 2152-67.

du Toit T et al. (2017) Profiling adrenal 11beta-hydroxyandrostenedione metabolites in prostate cancer cells, tissue and plasma: UPC2-MS/MS quantification of 11beta-hydroxytestosterone, 11keto-testosterone and 11keto-dihydrotestosterone. J Steroid Biochem Mol Biol. 166: 54-67.

Eisenhauer EA et al. (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 45 (2): 228-47.

EMA/CHMP/ICH/646107/2008. ICH guideline S9 on nonclinical evaluation for anticancer pharmaceuticals. Last updated https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-s9-non-clinical-evaluation-anticancer-pharmaceuticals-step-5_en.pdf

EMA/INS/GCP/532137/2010. Reflection paper for laboratories that peform the analysis or evaluation of clinical trial samples, 2012. Last updated

EMEA/CHMP/SWP/28367/07 Rev. 1. Guideline on strategies to identify and mitigate risks of first-in-human and early clinical trials with investigational medicinal products, 2017. Last updated http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/07/WC500232186.pdf

Ferlay J et al. (2013) Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 49 (6): 1374-403.

Fizazi K et al. (2016) Low incidence of corticosteroid-associated adverse events on long-term exposure to low-dose prednisone given with abiraterone acetate to patients with metastatic castration-resistant prostate cancer. Eur Urol. 70 (3): 438-44.

Halabi S et al. (2014) Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. J Clin Oncol. 32 (7): 671-7.

Heller G et al. (2018) Circulating Tumor Cell Number as a Response Measure of Prolonged Survival for Metastatic Castration-Resistant Prostate Cancer: A Comparison With Prostate-Specific Antigen Across Five Randomized Phase III Clinical Trials. J Clin Oncol. 36 (6): 572-580.

Isikbay M et al. (2014) Glucocorticoid receptor activity contributes to resistance to androgen-targeted therapy in prostate cancer. Horm Cancer. 5 (2): 72-89.

Jernberg E et al. (2017) Clinical relevance of androgen receptor alterations in prostate cancer. Endocr Connect. 6 (8): R146-R161.

Le Tourneau C et al. (2009) Dose escalation methods in phase I cancer clinical trials. J Natl Cancer Inst. 101 (10): 708-20.

Lorente D et al. (2014) Tumour responses following a steroid switch from prednisone to dexamethasone in castration-resistant prostate cancer patients progressing on abiraterone. Br J Cancer. 111 (12): 2248-53.

Loriot Y et al. (2013) Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Ann Oncol. 24 (7): 1807-12.

Mettler FA, Jr. et al. (2008) Effective doses in radiology and diagnostic nuclear medicine: a catalog. Radiology. 248 (1): 254-63.

Mitsiades N et al. (2012) Distinct patterns of dysregulated expression of enzymes involved in androgen synthesis and metabolism in metastatic prostate cancer tumors. Cancer Res. 72 (23): 6142-52.

Mostaghel EA et al. (2011) Resistance to CYP17A1 inhibition with abiraterone in castration-resistant prostate cancer: induction of steroidogenesis and androgen receptor splice variants. Clin Cancer Res. 17 (18): 5913-25.

Narayanan S et al. (2016) Androgen-glucocorticoid interactions in the era of novel prostate cancer therapy. Nat Rev Urol. 13 (1): 47-60.

Pretorius E et al. (2016) 11-ketotestosterone and 11-ketodihydrotestosterone in castration resistant prostate cancer: potent androgens which can no longer be ignored. PLoS One. 11 (7): e0159867.

Quinkler M et al. (2015) Mineralocorticoid substitution and monitoring in primary adrenal insufficiency. Best Pract Res Clin Endocrinol Metab. 29 (1): 17-24.

Romanel A et al. (2015) Plasma AR and abiraterone-resistant prostate cancer. Sci Transl Med. 7 (312): 312re10.

Scher HI et al. (2016) Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the prostate cancer clinical trials working group 3. J Clin Oncol. 34 (12): 1402-18.

Sharifi N (2015) Steroid sidestep: evading androgen ablation by abiraterone. Clin Cancer Res. 21 (6): 1240-2.

Simon R (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 10 (1): 1-10.

Stanbrough M et al. (2006) Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. Cancer Res. 66 (5): 2815-25.

UNSCEAR report (2000) Sources and effects of ionizing radiation. UNSCEAR 2000 report to the general assembly. United Nations Scientific Committee on the Effects of Atomic Radiation [UNSCEAR].

Yamada Y et al. (2016) Abiraterone acetate after progression with enzalutamide in chemotherapy-naive patients with metastatic castration-resistant prostate cancer: a multi-center retrospective analysis. BMC Res Notes. 9 (1): 471.

13. SUMMARY OF CHANGES TO AMENDMENT ~~11~~12

13.1 Revision history

Protocol and amendments	Date	Applies to
Clinical study protocol	31 October 2017	Global
Amendment 1	23 February 2018	UK
Amendment 2	2 March 2018	France
Amendment 3	15 November 2018	Global
Amendment 4	16 April 2019	Global
Amendment 5	05 September 2019	Global
Amendment 6	14 November 2019	Global
Amendment 7	6 November 2020	Global
Amendment 8	21 December 2020	Global
Amendment 9	8 March 2021	UK
Amendment 10	12 March 2021	France
Amendment 11	7 June 2021	Global
Amendment 12	25 October 2022	Global

13.2 Summary of changes

Tabular summary of changes is presented in Appendix 4.

14. APPENDICES

Appendix 1. Investigator signature

Appendix 2A. Management of adrenal insufficiency

Appendix 2B. Measures to prevent adrenal crisis

Appendix 2C. Instructions for adjusting replacement therapy with dexamethasone and fludrocortisone (added in Amendment 7)

Appendix 3. Applicable for part 1/phase 1 only: Glucocorticoid replacement therapy and gradual decrease to physiological dose after 4 weeks

Appendix 4. Summary of changes to Amendment ~~11~~12