Bone and joint disorders: screening and early clinical drug development

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CHAPTER 4

An exploratory first-in-man study to investigate the pharmacokinetics and safety of liposomal dexamethasone at a 2- and 1-week interval in patients with metastatic castration resistant prostate cancer

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ABSTRACT

AIM Dexamethasone has antitumour activity in metastatic castration resistant prostate cancer (mCRPC). We aimed to investigate intravenous liposome-encapsulated dexamethasone disodium phosphate (liposomal dexamethasone) administration in mCRPC patients.

METHODS In this exploratory first-in-man study, patients in part A received a starting dose of 10mg followed by 5 doses of 20mg liposomal dexamethasone at two-week intervals. Upon review of part A safety, patients in part B received 10 weekly doses of 18.5mg. Primary outcomes were safety and pharmacokinetic profile, secondary outcome was antitumour efficacy.

RESULTS Nine mCRPC patients (5 in part A, 4 in part B) were enrolled. All patients experienced grade 1-2 toxicity, one (part B) patient experienced grade 3 toxicity (permanent bladder catheter-related urosepsis). No infusion-related adverse events occurred. One patient had upsloping glucose levels ≤9.1mmol/L. Trough plasma concentrations of liposomal- and free dexamethasone were below the lower limit of quantification (LLOQ) in part A, and above LLOQ in 3 patients in part B ($t_{½}$ ~50h for liposomal dexamethasone), trough concentrations of liposomal- and free dexamethasone increased towards the end of the study. In seven out of 9 patients (78%) patients, stable disease was observed in bone and/or CT scans at follow-up, and in one (part B) of these 7 patients a >50% PSA biochemical response was observed.

CONCLUSIONS Bi- and once weekly administrations of IV liposomal dexamethasone were well tolerated. Weekly dosing enabled trough concentrations of liposomal- and free dexamethasone >LLOQ. The data presented support further clinical investigation in well-powered studies.

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Introduction

Prostate cancer is a highly prevalent disease in the elderly man.[1] Current first-line treatments of primary tumours, i.e. mainly surgery or radiotherapy, are effective in most patients with newly diagnosed apparent organ-confined prostate cancer. However, a considerable proportion of patients may develop incurable metastatic disease. Systemic treatment of advanced prostate cancer usually consists of multiple years of androgen deprivation therapy (ADT) which exerts its antitumour effect via chemical castration, but has a deleterious effect on bone health.[2–4] Once metastasized, bone is affected in ~90% of patients. At this stage, disease progression eventually occurs in almost all prostate cancer patients despite life-long ADT-induced castrate serum testosterone levels (castration-resistant prostate cancer, CRPC).

Corticosteroids have been widely used in the management of CRPC for over 30 years, as a monotherapy (daily orally administered) or combined with abiraterone, docetaxel or cabazitaxel.[5–9] In addition to their anti-inflammatory and anti-emetic effects, corticosteroids exhibit antitumour activity in mCRPC. This is attributed to the inhibition of adrenal androgen syntheses, through the CYP17A1, 17α-hydroxylase pathway.[10,11] Prednisone or prednisolone are most widely used. However, dexamethasone has a higher ratio of glucocorticoid to mineralocorticoid activity than prednisone, which may result in a better antitumour efficacy in CRPC patients.[12] Patients who switched from abiraterone plus prednisone to abiraterone plus 0.5mg dexamethasone daily, had a biochemical (PSA) response in 11-48% of the cases.[13–16]

Regardless of these advantages, long-term systemic exposure to corticosteroids is associated with serious toxicities such as adrenal insufficiency, immunosuppression, hypertension, oedema, Cushingoid habitus, hyperglycaemia and osteoporosis. Osteoporosis is of particular relevance in CRPC patients who already have numerous risk factors of developing bone health-related problems, including age, multiple osseous metastases and receiving life-long chemical castration through ADT.[17]

In general, liposomal delivery can reduce toxicity of the encapsulated drug, as it enables targeted drug delivery to the tumour sites.[18] Liposomes consist of a phospholipid- and cholesterol- bilayer, which can be modified with polyethyleneglycol (PEG). These so-called PEG-liposomes show a prolonged circulating half-life and improved targeting of tumour sites, due to the extravasation through leaky vasculature of solid tumour tissue.[19–21] The investigational product consists of the disodium phosphate derivate of

dexamethasone, which is encapsulated in the inner aqueous compartment of the PEG-liposomes (liposomal dexamethasone).[20] Both the sustained exposure and the targeting facilitated by liposomes are thought to benefit the antitumour efficacy of dexamethasone in liposomal dexamethasone.[22–25] In a preclinical xenograft model of experimental bone lesions from human prostate cancer, antitumour efficacy of treatment with free dexamethasone and liposomal dexamethasone were compared. A more potent and sustained antitumour effect was indeed found for liposomal dexamethasone.[19]

With this new liposomal dexamethasone formulation we envisage IV dosing at a dose level that gives equivalent plasma concentrations of free dexamethasone compared to those expected with the efficacious daily oral dose of 0.5mg dexamethasone, although local tumour exposure is expected to be higher as a result of targeted delivery.[12,15,26] Anticipating a long circulation half-life, it was decided to evaluate weekly and biweekly IV administrations of liposomal dexamethasone in a population of metastatic CRPC patients (mCRPC). The results of this exploratory first-in-man study with a focus on safety and PK are presented here.

Methods

PATIENTS

Men with documented mCRPC, who had received prior hormonal- and chemotherapy, and for whom no other treatment options were available according to the treating physicians, were eligible. Inclusion criteria (Supplemental Text 1) consisted of the presence of bone metastases, disease progression demonstrated by bone scintigraphy and/or computed tomography (CT) and progressive PSA levels, a castrate serum testosterone level of <50ng/dl or 1.7nmol/L at baseline and patients were not allowed to use systemic corticosteroids within 4 weeks prior to the first study drug administration. Potentially eligible patients from the Clinical Oncology department of the Leiden University Medical Center (LUMC), Leiden, The Netherlands, were referred to the Centre for Human Drug Research (CHDR), Leiden, The Netherlands, for further screening and enrolment. Screening took place after both verbal and written informed consent were obtained, and included collection of baseline characteristics from medical history, physical examination and, routine safety- and disease specific- laboratory assessments.

The study was approved by the medical ethics committee "Foundation Beoordeling Ethiek Biomedisch Onderzoek", Assen, The Netherlands, and was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization/WHO Good Clinical Practice standards. This trial was registered under international standard randomized controlled trials number (ISRCTN) 10011715 and EudraCT number 2016-003121-42.

STUDY DESIGN AND TREATMENT

This was a prospective, single centre, open label, exploratory first-in-man study of two dose regimens of liposomal dexamethasone in patients with mCRPC. The study consisted of parts A and B (Figure 1). In both parts, up to five patients were to be enrolled and were dosed with liposomal dexamethasone for 10 weeks. Treatments consisted of repeated IV administrations of liposomal dexamethasone diluted in 500mL NaCl 0.9% solution right before administration at the hospital pharmacy of the LUMC.

Doses were calculated based on the oral doses of prednisone, prednisolone and dexamethasone administered to mCRPC patients that are reported in literature (Supplemental Table 1).[5,7,12,15,27–31] The half-life was expected to be prolonged by the liposomes to 30-90h, as observed in clinical studies with other liposomal compounds.[31,32] Taking into account the PK, the drawback of IV dosing and the vulnerable mCRPC population, dose intervals of one to three weeks were deemed feasible from a pharmacokinetic- and operational perspective. Dose range for weekly- or biweekly liposomal dexamethasone administrations, equivalent to daily oral doses were calculated using molecular weights, (1 µg of dexamethasone disodium phosphate is hydrolysed to of 0.76µg free dexamethasone) and corticosteroid conversion tables from the Dutch national formulary and literature,[33,34] and ranged from 4.6 to 27.6mg dexamethasone disodium phosphate per 7 days, or from 9.2 to 55.3mg per 14 days.[5,6]

In part A, patients received a single 10mg dose of liposomal dexamethasone. After one week, a safety review meeting was held to decide if it was safe for the patient to proceed with the five additional doses of 20mg liposomal dexamethasone with two-week intervals. Based on the evaluation of the safety of part A, the dose and administration interval were adapted in part B to ten weekly doses of 18.5mg liposomal dexamethasone. The dose of 18.5mg was chosen as it was deemed appropriate from a PK and safety perspective and to enable dosing the patients from one batch of medication (ampoule contains 18.5mg). In both parts, patients remained in the clinical unit for at least 24 hours after the first and second study drug administrations for safety monitoring and regular PK sampling.

To prevent possible hypersensitivity reactions related to the IV administration of PEG-liposomes, a stepwise increase of the infusion rate (40min 0.05mL/min, 20 min 0.5mL/min, 97min 5mL/min) was applied and a Codan 1.2µm I.V.STAR® filter was used to prevent administration of liposome aggregates. Patients did not receive pre-treatment to prevent infusion reactions.

SAFETY

Patients were evaluated for adverse events during each visit and were asked to report those that had occurred between visits. To quantify potential infusion-related complement activation, the percentage of classic- and alternative pathway complement activation in plasma were measured by levels of membrane attack complex, and factors C1-4, B, H and I before and after the first dose. On pre-defined time points, safety laboratory (fasting blood chemistry, and haematology), vital signs and 12 lead electrocardiography were performed. The full schedule of assessments can be found in Supplemental Table 1. Adverse events (AEs) and serious adverse events (SAE) were registered and graded in accordance with the National Cancer Institute Common Terminology Criteria for AEs (CTCAE).[35]

PHARMACOKINETIC (PK) ANALYSES

While the liposomes contain dexamethasone disodium phosphate, it is anticipated that after *in vivo* target localization of the liposomes, the contents are released and rapidly hydrolysed to active dexamethasone.[34] *Ex vivo*, with part of the liposomes still intact in the circulation, this hydrolysis does not take place, and the free- and liposomal dexamethasone can thus be distinguished by *ex vivo* disruption of the liposomes and analysis of concentrations of both dexamethasone disodium phosphate (LLOQ 0.05 µg/mL) and dexamethasone (LLOQ: 0.005 µg/mL). All PK plasma concentrations were determined using a validated Liquid Chromatography-tandem Mass Spectrometry (LC-MS/MS) bioanalytical method.

Blood samples for PK analysis were obtained at baseline, and 1, 2, 3, 4, 6, 8, 12, 24 and 48 hours after the first two administrations. In part B, PK sampling was expanded with a 96-hour sample and samples right before each of the remaining study drug administrations to measure trough concentrations.

PK data were analysed by non-compartmental analysis in R (v3.6.1), using the PKNCA package.[36,37] The area under the curve (AUC) was calculated separately for dose 1 and dose 2 using the linear-up log-down method. The $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ were calculated to allow for correct comparison of the exposure to liposomal dexamethasone between weeks. For half-life calculation, the linear regression of the apparent terminal phase was reported if at least 3 points after the maximal concentration (C_{MAX}) were available, with a minimum r^2 of 0.85 and a span ratio of more than 1.5x the half-life.

PHARMACODYNAMICS (PD)

Pharmacodynamic endpoints included plasma concentrations of cortisol and fasting glucose, and lymphocyte counts; these were measured at baseline, after 3, 5, 7 and 9 weeks of treatment, and at the final follow-up visit.

ANTITUMOUR EFFECT

PSA plasma levels were measured at baseline and every four weeks. Plasma levels of haemoglobin, alkaline phosphatase and lactodehydrogenase (LDH) were measured at baseline, after 3, 5, 7 and 10 weeks of treatment, and at the final follow-up visit. Tumours were imaged at baseline and after 12 weeks using bone scintigraphy and/or computed tomography (CT) and evaluated for new lesions and size of existing lesions.

STATISTICS

As this was an exploratory trial with the primary aim of assessing safety and tolerability of liposomal dexamethasone, there was no formal power calculation and outcomes are presented descriptively.

Results

PATIENTS

Ten sequential patients with mCRPC were screened for this study of whom nine were enrolled: five patients in part A, four in part B. One patient was excluded based on limited life expectancy. All patients were enrolled between March 2017 and November 2018. Baseline characteristics are presented in Table 1. The median age of all patients was 70 years. All patients had at least two lines of pharmacological prostate cancer treatment prior to enrolment and no other treatment options were available according to the treating physicians. None of the patients had a diagnosis of diabetes. Eight patients completed all study drug administrations (in part A starting dose of 10mg followed by 5 two-weekly IV doses of 20mg liposomal dexamethasone, and in part B 10 weekly doses of 18.5mg liposomal dexamethasone). In part B, one patient did not receive the last dose. The study was stopped after 9 patients,

as the shelf life of the study drug was not long enough to ensure the tenth patient would receive the full treatment.

SAFETY

Infusion of liposomal dexamethasone was well tolerated and no infusion-related or hypersensitivity reactions were observed. This was confirmed by the absence of changes in the parameters used to assess the classic- or alternative pathway complement activation. A total of 19 treatment emergent AEs were observed in all 9 patients (Table 2), of which 18 were grade 1-2 (12 in part A). One possibly related grade 3 AE, urosepsis, was observed in a patient with an enhanced risk of infection due to a suprapubic bladder catheter and was accompanied by urine abnormalities, hypotension and increased LDH. The patient was admitted to the hospital to receive IV antibiotics, upon which his clinical condition rapidly improved. Due to this admittance, the last dose of liposomal dexamethasone was omitted. A non-related SAE (dyspnoea) was observed in another patient. The most frequently observed AEs (each of which occurred in 2 out of 9 patients (22%)) were infection, restlessness and postural dizziness. Except in relation to the urosepsis, no newly-emergent, clinically significant abnormalities in vital signs, ECG or safety laboratory outcomes, including liver- and renal toxicity- outcomes, occurred. No skeletal-related AEs were observed.

PHARMACOKINETIC RESULTS

A summary of the pharmacokinetics of liposomal dexamethasone and free dexamethasone after the starting dose of 10mg followed by a 20mg dose every two weeks (part A) and the weekly administration of a dose of 18.5mg (part B) is presented in Figure 2 and a tabular overview for liposomal dexamethasone and free dexamethasone is provided in Table 3. The plasma concentration of free dexamethasone was approximately 80-fold lower than that of the liposomal dexamethasone disodium phosphate. Due to the long plasma half-life of liposomal dexamethasone and the timing of the PK sampling, the plasma concentrations in two patients in part A reached insufficient span ratio to enable reliable calculation of $AUC_{0\text{-}inf}$, $t_{½}$, and clearance (Figure 2A,B, Table 3). The mean liposomal dexamethasone $t_{½}$ in the evaluable patients was 45.73 hours (range: 3.35-69.83). The mean distribution volume (V_Z) ranged 2.85 to 4.65L. In higher dose levels, the C_{MAX} was higher too, indicating dose dependency. In part B, trough concentrations (C_{trough}) for liposomal dexamethasone (Figure 2C) and free dexamethasone (Figure 2F) above the lower limit of detection were repeatedly observed in 3 out of 4 patients. C_{trough} for liposomal dexamethasone increased from 0.60 up to 1.26µg/mL over 9 weeks of dosing, indicating an accumulation of the liposomes upon subsequent dosing. In one patient (no 6) from part B, the liposomal dexamethasone plasma concentration curve deviates, with a much faster clearance and shorter elimination half-life than the other patients in part A and B.

PHARMACODYNAMIC EFFECTS

Fasting plasma glucose concentrations showed that one part B patient, with an already high baseline plasma glucose concentration (7.4 mmol/L) showed an increase in fasting plasma glucose concentrations up to 9.1mmol/L toward the end of the study. In all other patients, the glucose concentrations remained stable compared to baseline. In part A, plasma cortisol was not suppressed during the dosing period, whereas in group B, cortisol levels were suppressed from the first post-dose measurement onwards, with exception of patient 6 (Supplemental Figure 1).

ANTITUMOUR EFFECTS

Of the nine patients two (22%) patients, one in each part, had a decrease in PSA, of which one patient in part B showed a >50% PSA decrease at the 12-week visit, in one (11%) patient PSA was unchanged, whereas 6 (67%) patients had an increase in PSA (median 90.3%, range: 68.6 to 880%). LDH remained stable compared to baseline, except in two patients, in whom an increase of LDH occurred concurrent with the described SAEs. Haemoglobin was low in three patients from baseline onwards. No significant changes were observed in the alkaline phosphatase concentrations and lymphocyte counts. Radiological evaluation by bone and/or CT scan at 3 months, indicated progressive disease in two patients (one in part A, one in part B), and stable disease in the remaining 7 patients. No additional follow-up scans within the context of this study were done precluding confirmation of radiological responses.

Discussion

We report here the results of an exploratory first-in-man study for safety and PK, in which 9 patients with mCRPC received 10 weeks of IV treatment with an experimental PEG-liposomal formulation of dexamethasone. In this group administration of liposomal dexamethasone was found to be well

tolerated with few grade 1-2 toxicities and similar AEs compared to a study of daily 0.5mg oral dexamethasone in a CRPC patient group.[12] Importantly, no infusion reactions during or immediately after infusion of the liposomes occurred, as was reported in previous studies.[38,39] For the administration of liposomal dexamethasone we used a stepwise increase of the infusion rate and a filter to prevent administration of liposome aggregates (Figure 1), which may both have contributed to the absence of any infusion related adverse event. Patients did not receive pre-treatment to prevent infusion reactions.

Although the administrations were found to be safe, one possibly treatment-related grade 3 adverse event occurred, which was a urosepsis in a patient at risk of developing urogenital infections due to the presence of a suprapubic catheter. Otherwise, treatment emergent adverse events were mild in severity and most were transient of nature. No bone-related AEs were observed. Fasting glucose remained stable except in the (part B) patient with the highest baseline glucose plasma in whom glucose concentrations increased during the study. This merely underscores the known importance of close monitoring of glucose levels during treatment with corticosteroids.[17,40]

In part A of the study, the trough level of liposomal- and free dexamethasone prior to the second study drug administration was below the LLOQ in all subjects. As no trough samples were obtained prior to the third- and following doses, accumulation and plasma concentrations above the LLOQ at later time points cannot be ruled out. However, the absence of cortisol suppression during the dosing period seen in this group also suggests that a biweekly dosing interval is safe but does not provide the preferred continuous exposure.

Using the dose regimen as in part B of the study, repeated trough concentrations above LLOQ for liposomal- and free dexamethasone, which gradually increased over time, were measured. The PK analysis clearly shows that at multiple time points during treatment liposomal encapsulated as well as free dexamethasone levels above LLOQ and cortisol suppression are achieved after weekly doses of liposomal encapsulated dexamethasone.

Hochhaus et al.[41] have studied the PK after IV administration of 10mg dexamethasone disodium phosphate in young healthy men. The authors report a mean relative AUC in this study of 57 µg/l*h per administered mg of dexamethasone disodium phosphate. We found a similar exposure with the liposomal dexamethasone disodium phosphate formulation, with AUCs in the range of 46.9 to 56.7µg/l*h for each administered mg. In another study by Spoorenberg et al.[42], enrolling patients hospitalized with community acquired pneumonia, a (>2-fold) higher AUC per gram dose was found. This difference is thought to be caused by slower clearance in this specific patient population.[42]

The liposomal formulation proved effective in prolonging the half-life of dexamethasone, to approximately 2 days (medians of 43-48 hrs), whereas free dexamethasone has a t½ of 3-5 hours.[34,41] This half-life is comparable to that of other PEG-liposomal compounds.[31,32] Due to the length of the t½ and the PK sampling schedule, a reliable calculation of the t½ could only be done for three patients of part A. The two other patients appeared to have a longer t½, but these values cannot be calculated reliably, as the sampling period was too short. Hence, we currently underestimate the t½ in our outcomes. In part B, a 96h PK sample and trough samples for study drug administrations 2 to 10 were added to the sampling schedule to enable calculation of all PK parameters. The half-life of liposomal dexamethasone varied between subjects, with patient 6 being a clear outlier (Figure 2B, D). In this patient, the half-life was only three hours, which implicates a fast breakdown of the PEGylated liposomes, resulting in a short, high exposure to dexamethasone. Accelerated blood clearance of liposomes has been described after preceding liposome administrations, but in this case fast clearance was already observed following the first administration in this liposome-naïve patient.[43] We do not have a mechanistic explanation for this apparent rapid liposomal degradation as we did not find any peculiarities in patient's previous anti-cancer treatments, concomitant medication, laboratory outcomes, leukocyte or monocyte count, or adverse events.

The distribution volume ranged between 2.85 to 4.65L, which is comparable to the plasma volume. The half-life and distribution volume indicate that the majority of liposomal dexamethasone (dexamethasone disodium phosphate) resides in the circulation until organ uptake, subsequent release of the drug from the liposome and hydrolysis to dexamethasone. This process creates a slow release system; explaining the relatively low C_{MAX} and long half-life. Although not measured in this clinical trial, pre-clinical trials support the hypothesis that tumours preferentially take up liposomes and are exposed to relatively high and persisting free dexamethasone concentrations upon release from the liposomes.[19] With this tumour targeting and the relatively low systemic concentrations of free dexamethasone that were observed in this study in mind, one can envisage an enhanced efficacy over safety ratio, which remains to be confirmed in future phase 2 studies.

The absence of cortisol suppression during the dosing period seen in group A patients (although identified after the 3-month treatment period) underscores that a two-week dosing interval of 20mg liposomal dexamethasone is safe. In part B the rapid decline and sustained suppression of endogenous cortisol during the dosing period and demonstrable free dexamethasone concentrations in the blood, is in agreement with the suppression of the cortisol-axis commonly observed during systemic corticosteroid treatment. The PK and PD cortisol axis-suppression data observed following weekly administration of 18.5mg of liposomal-encapsulated dexamethasone in combination with the biochemical PSA and radiological antitumour responses, suggest that a follow-up study using weekly i.v. administrations of liposomal encapsulated dexamethasone is most promising.

This exploratory clinical study focussed on safety and PK, and was not powered, nor set-up to assess antitumour efficacy of liposomal dexamethasone. Hence limitations of the study are the small sample size, and the short period of treatment and follow-up before the biochemical and radiological efficacy evaluations were done. By design, this precludes drawing firm conclusions about the true antitumour efficacy. In one patient, a biochemical response was measured. Although this is a limited effect, this outcome should be seen in the perspective of the study population: end-stage CRPC patients, who had had multiple lines of treatment prior to enrolment.

Future studies with this compound should enrol and evaluate a larger number of patients, in an earlier stage of disease progression, for a longer follow-up period. These studies should explore different dosing regimens, starting at weekly 18.5mg doses, or slightly lower, based on the current study. In addition, methods to investigate the delicate balance between optimal delivery of the liposomal encapsulated drug at the site of metastases and systemic release of free drug methods should be integrated. The use of PET fluorescence- or radio-labelled liposomal dexamethasone could confirm whether liposomal encapsulated dexamethasone indeed (preferentially) targets the tumour sites as has been observed in our animal model.[19] With preliminary safety shown in a vulnerable patient population, these efficacy and target localization studies are now warranted.

In conclusion, IV administration of liposomal dexamethasone was well tolerated in this small group of mCRPC patients. The safety- and pharmacokinetic profile of weekly IV administered liposomal dexamethasone support further trials to investigate the targeting and efficacy of liposomal dexamethasone in well-powered experiments, and the possibility of combination with other anticancer agents.

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Table 1 Baseline patient and disease characteristics

Patient characteristics	Total group N=9	Part A N=5	Part B N=4
AGE (YEARS)			
At enrolment, median (range)	70 (61-77)	67 (61-74)	73 (70-77)
At disease onset, median (range)	65 (52-75)	61 (52-67)	68 (65-75)
WEIGHT (KG) median (range)	93.5 (74.8-118.4)	101.4 (93.5-118.4)	90.0 (74.8-93.5)
HEIGHT (CM) median (range)	178.2 (169-193)	180.3 (178.2-193.2)	175.4 (169.0-176.0)
BMI (KG/M^2) median (range)	29.9 (24.0-36.4)	31.2 (27.1-36.4)	29.3 (24.0-32.7)
BASELINE BLOOD PLASMA CONCENTRATIONS			
Haemoglobin, mmol/L median (range)	7.0 (5.8-9.8)	7 (5.8-9.8)	6.7 (5.8-8.0)
Alkaline phosphatase, U/L median (range)	152 (58-313)	152 (110-261)	147 (58-313)
Lactate dehydrogenase, U/L median (range)	200 (169-425)	180 (169-220)	257 (181-425)
TIME EXPIRED (MONTHS)			
Initial diagnosis to enrolment, median (range)	62 (28-113)	85 (42-113)	37 (32-104)
CRPC to enrolment, median (range)	22 (10-49)	22 (14-49)	22 (10-35)
ECOG PERFORMANCE SCORE			
0, N (%)	1 (11)	0 (0)	1 (25)
1, N (%)	6 (67)	4 (80)	2 (50)
2, N (%)	2 (22)	1 (20)	1 (25)
PSA (ug/L)			
Baseline median (range)	17.1 (4.4-424.4)	72.9 (9.2-213.6)	160.3 (4.4-424.4)
PSA BEFORE FIRST HORMONE THERAPY (ug/L)			
Median (range)	27.3 (9.2->1100)	23 (9.2-186)	56 (12.8->1100)
PREVIOUS LINES OF TREATMENT			
LHRH agonist/previous ADT (+/- bicalutamide), N (%)	9 (100)	5 (100)	4 (100)
Enzalutamide, N (%)	8 (89)	4 (80)	4 (100)
Abiraterone + prednisone, N (%)	1 (11)	1 (20)	0 (0)
Docetaxel + prednisone, N (%)	6 (67)	3 (60)	3 (75)
Cabazitaxel +prednisone, N (%)	3 (33)	1 (20)	2 (50)
Radium-223 (%)	3 (33)	2 (40)	1 (25)

BMI, body mass index. ECOG, eastern cooperative oncology group. PSA prostate specific antigen LHRH, luteinizing hormone releasing hormone. ADT, androgen deprivation therapy

Table 2 Treatment emergent adverse events graded according the National Cancer Institute Common terminology criteria for Adverse events (CTCAE) version 5.0.

Adverse event	Part A (1 × 10mg + 5 × 20mg)		Part B (10 × 18.5mg)	
	Grade 1-2 N (%)	Grade 3-4 N (%)	Grade 1-2 N (%)	Grade 3-4 N (%)
Any adverse event	5 (100)	0 (0)	4 (100)	1 (25)
All infections	0 (0)	0 (0)	1 (25)	1 (25)
Postural dizziness	1 (20)	0 (0)	1 (25)	0 (0)
Fatigue	2 (40)	0 (0)	0 (0)	0 (0)
Restlessness	1 (20)	0 (0)	1 (25)	0 (0)
Hypertension	0 (0)	0 (0)	1 (25)	0 (0)
Oedema	0 (0)	0 (0)	1 (25)	0 (0)
Cancer related pain	1 (20)	0 (0)	0 (0)	0 (0)
Hot flashes	1 (20)	0 (0)		
Skin atrophy	1 (20)	0 (0)	0 (0)	0 (0)
Presyncope	1 (20)	0 (0)	0 (0)	0 (0)
Proteinuria	1 (20)	0 (0)	0 (0)	0 (0)
Urine incontinence	1 (20)	0 (0)	0 (0)	0 (0)
Dysgeusia	1 (20)	0 (0)	0 (0)	0 (0)
Hyperglycaemia	0 (0)	0 (0)	1 (25)	0 (0)
Confused state	0 (0)	0 (0)	1 (25)	0 (0)
Infusion reaction	0 (0)	0 (0)	0 (0)	0 (0)
Influenza like illness	0 (0)	0 (0)	0 (0)	0 (0)
Pyrexia	0 (0)	0 (0)	0 (0)	0 (0)
Nausea/vomiting	0 (0)	0 (0)	0 (0)	0 (0)
Hypotension	0 (0)	0 (0)	0 (0)	0 (0)
Anaemia	0 (0)	0 (0)	0 (0)	0 (0)
Leukopenia	0 (0)	0 (0)	0 (0)	0 (0)
(febrile) Neutropenia	0 (0)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	0 (0)	0 (0)	0 (0)	0 (0)
ASAT increase	0 (0)	0 (0)	0 (0)	0 (0)
ALAT increase	0 (0)	0 (0)	0 (0)	0 (0)
Bilirubinaemia	0 (0)	0 (0)	0 (0)	0 (0)
Asthenia	0 (0)	0 (0)	0 (0)	0 (0)

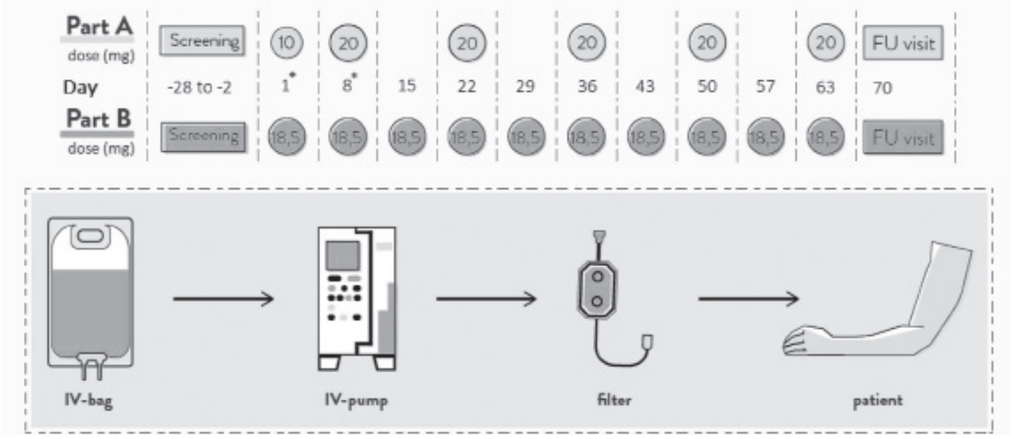
ASAT aspartate aminotransferase, ALAT alanine aminotransferase

Table 3 Summary of PK parameters for A. liposomal dexamethasone and B. free dexamethasone.

A. Liposomal dexamethasone (dexamethasone disodium phosphate)				
	Part A		**Part B**	
Dose 1	**PK 10mg**		**PK 18.5mg**	
	Mean (SD)	**range**	**Mean (SD)**	**range**
C_{MAX} (µg/mL)	2.392 (0.520)	1.70-2.99	4.45 (1.07)	2.93-5.22
T_{MAX} (h)	3.0[a]	3.0-3.0	3.0[a]	3.0-3.0
AUC_{INF} (h*µg/mL)	209.5 (57.4)[b]	149-263[b]	354.5 (259.4)	19.3-600
AUC_{LAST} (h*µg/mL)	142 (71.1)	60.2-234	297 (203)	19-483
CL (L/h)	0.050 (0.015)[b]	0.038-0.067[b]	0.27 (0.46)	0.031-0.96
Vz (L)	3.34 (0.43)	2.85-3.66	3.6 (0.72)	3.11-4.65
$T_{½}$ (h)	47.7 (10.0)[b]	36.22-54.8[b]	43.4 (31.0)	3.35-69.8
Dose 2	**PK 20mg**		**PK 18.5mg**	
	Mean (SD)	**range**	**Mean (SD)**	**range**
C_{MAX} (µg/mL)	5.02 (0.96)	3.65-6.36	4.99 (2.21)	1.98-6.84
T_{MAX} (h)	4.0[a]	3.0-4.0	3.5	3.0-6.0
AUC_{LAST} (h*µg/mL)	179 (47.1)	124-246	347 (257)	4.34-573
$T_{½}$ (h)	- [c]	- [c]	54.0 (15.2)	44.5-71.6[b]
B. Free dexamethasone (dexamethasone)				
	Part A		**Part B**	
Dose 1	**PK 10mg**		**PK 18.5mg**	
	Mean (SD)	**range**	**Mean (SD)**	**range**
C_{MAX} (µg/mL)	0.023 (0.012)	0.012-0.041	0.032 (0.021)	0.013-0.053
T_{MAX} (h)	8.0[a]	4.0-12.0	8.0[a]	6.0-23.2
AUC_{LAST} (h*µg/mL)	0.421 (0.305)	0.091-0.904	0.660 (0.610)	0.188-1.56
Dose 2	**PK 20mg**		**PK 18.5mg**	
	Mean (SD)	**range**	**Mean (SD)**	**range**
C_{MAX} (µg/mL)	0.062 (0.033)	0.032-0.112	0.047 (0.032)	0.016-0.080
T_{MAX} (h)	11.0[a]	8.0-12.0	8.5[a]	6.0-12.0
AUC_{LAST} (h*µg/mL)	1.61 (0.942)	0.83-3.09	1.8 (1.18)	0.70-3.47

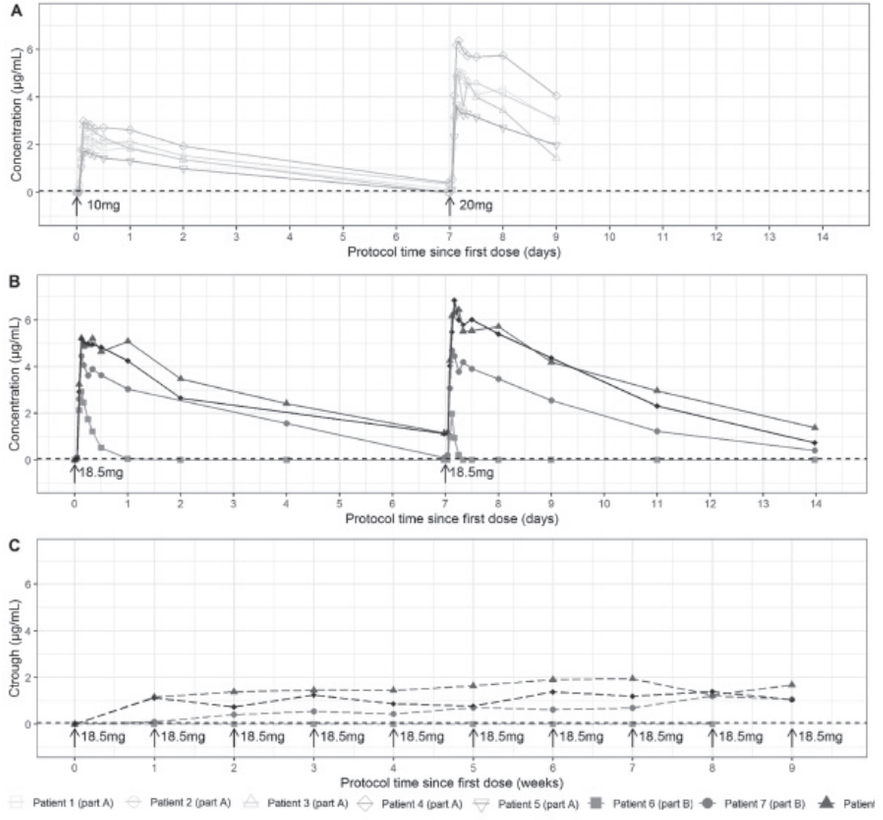
a Median
b Value based on measurements in three patients
c $T_{½}$ could not be calculated as trough samples were not obtained prior to dose 3

Figure 1 Study design and set-up for study drug administration Study design and set-up for study drug administration. After evaluation of the PK and PD results.



** After the drug administrations of weeks 1 and 2, patients stayed overnight in the clinic for safety monitoring and PK sampling*

Figure 2 PK panel liposomal dexamethasone (dexamethasone disodium phosphate) and free dexamethasone (dexamethasone) PK of liposomal dexamethasone disodium phosphate (liposomal dexamethasone) and free dexamethasone for groups A (panels A and D) and B (panels B and E), after the first administration (up to day 7) and second administration (from day 7 onwards). For part B, PK sampling was adjusted by adding samples on days 4, 11 and prior to the remaining study drug administrations, enabling a more complete PK profile and plots of the trough concentrations (panels C and F). Trough concentrations were above the LLOQ and ascending trends of the trough concentrations were measured toward the end of the study in all patients except nr. 6. In patient 6, a rapid clearance of liposomal- and free dexamethasone is observed, seen as a rapid decrease of the liposomal dexamethasone concentration (panels B and E). The plasma molarity of the inactive liposomal dexamethasone disodium phosphate was approximately 80-fold higher than that of the free (active) dexamethasone.



(Continuation Figure 2)