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Clinical Trial

# A randomised, double-blind, dose-finding, phase II multicentre study of ODX in the treatment of patients with castration-resistant prostate cancer and skeletal metastases

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**KEYWORDS**
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**Abstract** ***Aims:*** This study aimed to assess the efficacy and safety of ODX, a novel, cytotoxic, bone-targeting drug candidate, in castration-resistant prostate cancer bone metastatic disease.
***Methods:*** Patients with progressive disease were randomised to ten cycles of ODX, intravenous infusion Q2W (3, 6, and 9 mg/kg, respectively). The primary objective was to assess

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ODX

the relative change from baseline in bone alkaline phosphatase (B-ALP) and serum-amino-terminal-propeptide of Type I procollagen (S-P1NP) at 12 weeks. The inclusion criteria selected were broad, and a double-blind design was used to ensure objective recruitment of patients for the assessment of efficacy. None of the patients received bone-protecting agents during the ODX treatment period.

***Results:*** Fifty-five 21,20 and 14) patients were randomised to ODX (3, 6 and 9 mg/kg), respectively. The lower number of patients in arm 3 was due to too low a recruitment rate towards the end of the study. The median treatment time were 14, 13 and 14 weeks, respectively. The decrease in B-ALP at 12 weeks in study arms 3, 6 and 9 mg/kg was seen in 6/15 (40%), 8/12 (67%) and 5/12 (42%) patients, respectively, whereas the corresponding numbers for P1NP were 8/15 (53%), 8/12 (67%), and 4/12 (33%), respectively. The median decrease in B-ALP and P1NP at 12 weeks for study arms 3, 6 and 9 mg/kg were 37%, 14% and 43%, respectively, and 51%, 40% and 64%, respectively. The decrease in serum C-terminal telopeptide at 12 weeks was seen in the vast majority of patients and in about one-third of patients in bone scan index. ODX was well tolerated, and no drug-related serious adverse events occurred. There were no significant differences between study arms regarding efficacy and safety.

***Conclusions:*** ODX was well tolerated and demonstrated inhibitory effects on markers related to the vicious cycle in bone at all three doses. The reduction in metastatic burden, assessed with bone scan index, supports this finding. Studies with continued ODX treatment until disease progression are being planned (ClinicalTrials.gov Identifier: NCT02825628).



## 1. Introduction

More than 90% of patients with mCRPC have skeletal metastases at an early stage [1]. These are the major cause of decreased quality of life (QoL) and death [2–4]. None of the existing CRPC drugs [5] and none of the bone-protecting agents (BPAs), which are now part of standard of care [6–10], is curative. Bone-targeted radionuclide treatment of metastatic castration-resistant prostate cancer (mCRPC) with Radium-223-dichloride has proven effective in curbing disease progression and prolonging overall survival (OS) [11]. The effect is mainly executed by its interruption of the vicious cycle in bone metastases, that is, the deleterious process that takes place between tumour cells, osteoclasts and osteoblasts [12]. ODX is a novel, cytotoxic, non-radioactive, drug candidate that targets bone metastases and, in analogy with Radium-223-dichloride, inhibits the vicious cycle. ODX comprises a dextran backbone, conjugated with guanidine (cytotoxic moiety) and alendronate (bone targeting moiety) [13]. A phase I trial in mCRPC patients (NCT01595087) demonstrated good tolerability [14]. The aim of the present study was to assess its efficacy and safety at three dose levels. The broad inclusion criteria chosen allowed assessment in treatment-naïve patients as well as patients who had undergone one or more CRPC therapy. A maximum of ten cycles was deemed sufficient to assess efficacy and to monitor safety. Assessment of bone markers is in line with the endpoints used in previous trials on Radium-223-dichloride [15,16]. The phase I trial implemented 3 mg/kg. In the current trial, 6 and 9 mg/kg were added mainly to assess safety parameters. The inclusion criteria chosen were broad. The double-blind design ensured the objective recruitment of patients for the assessment of efficacy. Bone scan index (BSI) was used for a quantitative assessment of antitumoral effects on bone metastatic burden [17,18].

## 2. Methods

### 2.1. Study design

This randomised, double-blind, dose-finding, repeat-dose, multicentre, phase II study evaluated the efficacy and tolerability of three different doses of ODX (3.0, 6.0 and 9.0 mg/kg). Fifty-five patients were enrolled at eight centres (Estonia, Finland, Latvia and Sweden). Each patient was to receive ODX at 2-week intervals, with a maximum of ten doses or until disease progression or unacceptable toxicity occurred. A final examination was conducted at 2 weeks after the last administration of ODX with long-term telephone follow-ups (FUs) at 3-month intervals (for up to 2 years) to assess OS.

Eligible patients were first randomised to one of the two lower ODX dose groups (3.0 and 6.0 mg/kg, respectively; 12 patients per treatment group). As soon as the 24th patient had been randomised, inclusion of patients to any of the treatment groups was placed on hold, and an Independent Data Monitoring Committee meeting was conducted. The Independent Data Monitoring Committee found no safety concerns, and, therefore, randomisation to all three treatment groups was permitted (Online Supplement: Fig. S1, and Allocation and

Blinding). The trial was discontinued at 55 patients because of too low a recruitment rate towards the end of the study period. This resulted in 14 patients, instead of the expected 20, in the 9 mg/kg arm (Fig. 1). The primary objective was to evaluate the relative change from baseline in response markers related to bone metabolism, that is, bone alkaline phosphatase (B-ALP) and serum-aminoterminal-propeptide of Type I procollagen (S-P1NP), after 12 weeks of treatment with either one of the three ODX doses (3.0, 6.0 and 9.0 mg/kg). Among the secondary objectives are progression-free survival (PFS), OS, change from baseline in serum C-terminal telopeptide (S-CTX), osteocalcin, prostate-specific antigen (PSA), and bone metastatic burden using BSI.

### 2.2. Patient enrolment

Eligible patients were males aged ≥18 years with histologically or cytologically confirmed prostate cancer and radiographic evidence of bone metastases (with or without soft tissue metastases), evidence of progressive disease in bone and/or evidence of PSA progression according to Prostate Cancer Working Group 3 (PCWG3) criteria and castrate levels of serum testosterone (≤1.7 nmol/L). Patients on lutenising hormone-releasing hormone (LHRH) agonists continued with these during the study treatment. Eastern Co-operative Oncology Group performance status 0–2 and adequate haematologic, hepatic and renal function parameters were used. Concurrent use of other anticancer agents or treatments was not allowed, with the exception of continued castration therapy. The main exclusion criteria were known brain metastases, dental surgery/extraction within 6 months before the first ODX dose; bisphosphonate/denosumab within 4 w prior to, and throughout, treatment period.

### 2.3. Study procedures

#### 2.3.1. Treatment

After infusion with 20 ml (150 mg/ml) of Dextran 1 (Promiten), ODX was administered as a slow IV infusion, 250 ml, at 2-week intervals, with a maximum of ten doses or until progressive disease, unacceptable toxicity or withdrawal according to the clinical study protocol.

### 2.4. Bone scintigraphy and computed tomography

Bone scans were performed according to European Association of Nuclear Medicine bone scintigraphy procedure guidelines and PCWG3 at screening, after 3 months and at 2 weeks after the last treatment (Follow-Up 1, FU1). Eligible bone scans were evaluated quantitatively with BSI using the software package EXINI scan index (EXINI Diagnostics, Lund, Sweden). Computed tomography was performed in accordance with RECIST at screening, after 3 months, and at FU1.

### 2.5. QoL and pain

QoL and pain were assessed with the FACT-P and EQ-5D-5L questionnaires [19,20].

### 2.6. Clinical safety assessments

Safety data were monitored from the screening visit until FU1. Definition and handling of adverse event (AE), serious AE (SAE), adverse drug reaction, serious adverse drug reaction, and Suspected Unexpected Adverse Reaction according to standard clinical trial practice. Severity classified according to CTCAE, version 4.03.

### 2.7. Sample size and statistics

For this study, a working sample size of 20 per group should be sufficient to enable the detection of a 20% difference in the relative change in B-ALP and S-P1NP, assuming a power of 80%, a two-sided significance level of 5% and a standard deviation of 20%. The analysis of primary efficacy was based on the full analysis set (FAS) and per protocol set. For the primary endpoint, analysis of variance including the factor treatment was used. The analysis of all secondary efficacy parameters was performed with the FAS. Safety analysis was based on safety analysis set. Time to event analyses medians and 95% confidence intervals were calculated from PROC LIFETEST output using the Brookmeyer and Crowley method; 95% confidence interval was calculated for relative change from baseline median without distribution assumption.

## 3. Results

### 3.1. Baseline patient and disease characteristics

From September 2016, a total of 55 patients were randomised at eight study centres in four countries until June 2018, and FU of OS data took place 2 years after the last treatment in June 2020. Demographic and baseline disease characteristics were well balanced between the three treatment arms (Table 1). One patient did not start treatment, and thus, 54 patients were treated and included in FAS. Prior therapy with docetaxel, cabazitaxel, abiraterone, enzalutamide, and Radium-223-dichloride had been administered to 28 of 54 (52%) patients. One line of therapy in 6 of 54 (11%) patients, two lines in 9 of 54 (17%), three lines in 9 of 54 (17%), and four lines in 4 of 54 (7%). Fourteen patients had previously received zoledronate and/or denosumab (see Online Supplement, Table S3). In line with protocol inclusion criteria, none of the patients received BPAs during the ODX treatment period. Twenty-eight patients (52%) completed all ten treatment cycles (18 weeks) with the study drug (Fig. 1). The most common

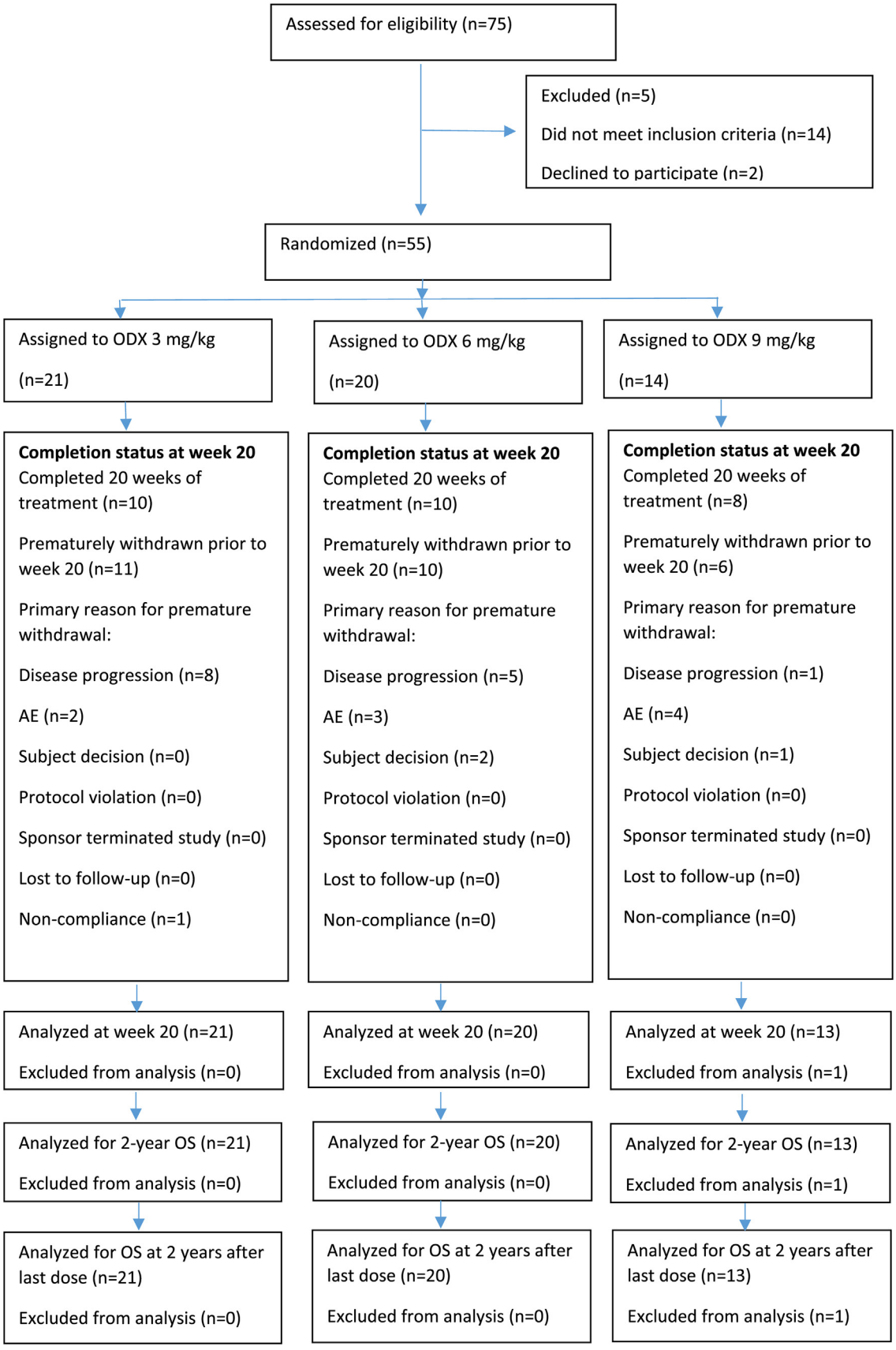


Fig. 1. Patient disposition. The diagram depicts the flow of patients in the study.

Table 1
Baseline patient demographics and characteristics.

| | 3.0 mg/kg ODX (n = 21) | 6.0 mg/kg ODX (n = 20) | 9.0 mg/kg ODX (n = 14) | Stat.[a] |
|---|---|---|---|---|
| Age, years (mean, range) | 72 (56–83) | 67 (55–80) | 70 (58–82) | NS |
| Haemoglobin, g/l (median, range) | 131.0 (114–154) | 123.0 (92–150) | 126.5 (91–159) | NS |
| Albumin, g/l (median, range) | 40.0 (31.0–50.0) | 40.0 (26.0–49.0) | 41.5 (27.0–51.9) | NS |
| Lactate dehydrogenase, ukat/l, (median, range) | 6.1 (2.67–18.22) | 4.5 (2.97–13.00) | 6.5 (2.87–15.60) | NS |
| PSA, ug/l (median, range) | 57 (1–3572) | 84 (2–1449) | 71 (3–2426) | NS |
| ALP, ukat/l (median, range) | 1.8 (0.8–16.5) | 2.3 (1.0–8.8) | 2.3 (0.94–16.3) | NS |
| P1NP, ug/l (median, range) | 112 (32–1590) | 133 (14–426) | 124 (19–1560) | NS |
| CTX, ng/l (median, range) | 472 (17–2540) | 537 (17–1765) | 398 (17–1615) | NS |
| Bone metastases (n, %) | | | | NS |
| <5 | 5 (23.8) | 1 (5.0) | 3 (21.4) | |
| 5–20 | 10 (47.6) | 8 40.0) | 5 (35.7) | |
| >20 | 5 (23.8) | 11 (55.0) | 5 (35.7) | |
| PAIN (FAC023 I have aches/pains that bother me, 0–4), mean ± SD | 2.0 ± 1.12 | 2.4 ± 1.12 | 2.2 ± 1.48 | NS |
| Prior CRPC therapies with OS benefit | | | | NS |
| None | 12 (57.1) | 7 (35.0) | 7 (50) | |
| Docetaxel | 8 (38.1) | 10 (50.0) | 8 (57.1) | |
| Cabazitaxel | 3 (14.3) | 4 (20.0) | 2 (14.3) | |
| Abiraterone | 4 (19.0) | 2 (10.0) | 6 (42.9) | |
| Enzalutamide | 3 (14.3) | 7 (35.0) | 2 (14.3) | |
| Radium-223 | 1 (4.8) | 3 (15.0) | 2 (14.3) | |

Note: 'FAC023 – I have aches/pains that bother me' scale is 0–4, where 0 means 'Very much' and 4 means 'Not at all'.
[a] NS, not statistically significant (no statistically significant difference between any group).

reasons for discontinuation (27 patients) were disease progression (14/27 [52%]) and AEs (9/27 [33%]). There were no drug-related SAEs. One patient was excluded from the analysis because of the withdrawal of consent. All patients (n = 54) were included in the OS analysis 2 years after the last treatment. Patients still alive 2 years after the last treatment numbered 21/54 (39%).

The total number of doses administered were as follows: Arm 3 mg/kg: 164/210 (78.1%); Arm 6 mg/kg 150/200 (75%); and Arm 9 mg/kg 110/140 (79.3%). The median number of cycles was seven for the three arms. The median duration of treatment (weeks) were 13.6, 13.4 and 14.4 for Arms 3, 6 and 9 mg/kg, respectively.

### 3.2. Efficacy outcomes

Treatment responses at 12 weeks with decline from baseline in B-ALP were as follows: Arm 3 mg/kg, 6/15 (40%) of patients; Arm 6 mg/kg, 8/12 (67%) of patients; Arm 9 mg/kg, 5/12 (42%) of patients (Fig. 2a). Treatment response with decrease in S-P1NP from baseline: Arm 3 mg/kg, 8/15 (53%) of patients; Arm 6 mg/kg, 8/12 (67%) of patients; and Arm 9 mg/kg, 4/12 (33%) of patients (Fig. 2b). The median response values (percent decrease at 12 weeks) for each dose arm are presented in Table 2. There were no statistically significant differences between the three arms.

The main secondary variables are summarised in Table 2: assessment of PFS was performed 2 weeks after the last ODX dose, and the maximum number of doses allowed was ten. The median PFS for the dose arms 3.0, 6.0 mg/kg was 20 and 22 weeks, respectively; not reached for dose arm 9.0 mg/kg. There were no statistically significant differences between the three arms. Assessment of OS was done at 2 years after the last ODX dose. The median OS was not reached for dose arm 3.0 mg/kg, whereas it was 47 and 102 weeks for arms 6.0 and 9.0 mg/kg, respectively. There were no statistically significant differences between the three arms.

The most pronounced effect was seen in CTX, a marker reflecting the activity of osteoclasts, the main target for ODX. Treatment response at 12 weeks with decline from baseline: Arm 3 mg/kg, 13/15 (87%) of patients; Arm 6 mg/kg, 8/12 (67%) of patients; Arm 9 mg/kg, 7/12 (58%) of patients (Fig. 2c). There were no statistically significant differences between the three arms. Treatment response with decrease from baseline in S-Osteocalcin at 12 weeks: Arm 3 mg/kg, 12/15 (80%) of patients; Arm 6 mg/kg, 7/12 (58%) of patients; Arm 9 mg/kg, 5/12 (42%) of patients. There were no statistically significant differences between the three arms. A decline in PSA at 12 weeks was seen in 5/39 (13%) patients (data not shown).

The median response values at 12 weeks for change from baseline in S-CTX and S-Osteocalcin are summarised in Table 2.

Treatment response with decrease from baseline in BSI at 12 weeks: Arm 3 mg/kg, 3/12 (25%) patients; Arm 6 mg/kg, 6/12 (50%) patients; Arm 9 mg/kg, 3/9 (33%) patients. There were no statistically significant differences between the three arms (Fig. 2d). The median response values for each dose arm are presented in Table 2. Four of the 12 (33%) BSI responders had

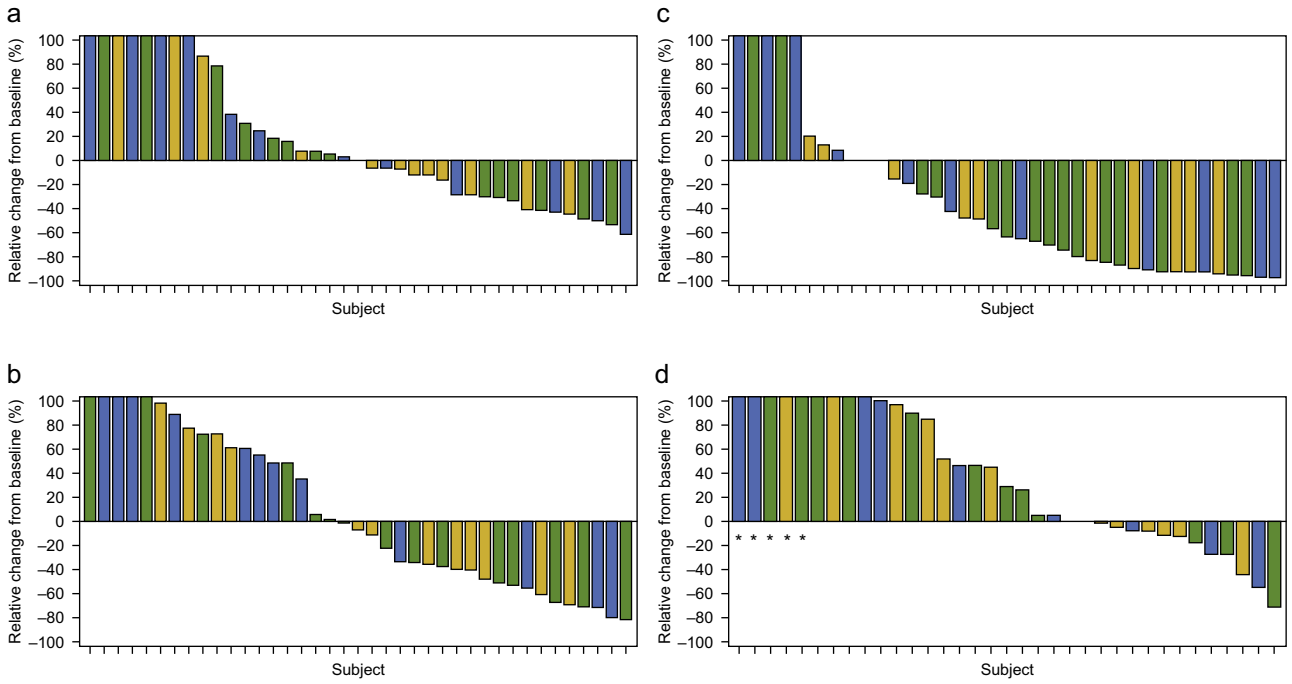


Fig. 2. (a) B-ALP, percent change from baseline at week 12. Green, yellow and blue bars denote ODX 3.0 mg/kg, ODX 6 mg/kg and ODX 9.0 mg/kg, respectively. Values over 100 were truncated. (b) S-P1NP, percent change from baseline at week 12. Green, yellow and blue bars denote ODX 3.0 mg/kg, ODX 6 mg/kg and ODX 9.0 mg/kg, respectively. Values over 100 were truncated. (c) S-CTX, percent change from baseline at week 12. Green, yellow and blue bars denote ODX 3.0 mg/kg, ODX 6 mg/kg and ODX 9.0 mg/kg, respectively. Values over 100 were truncated. (S-CTX reflects the activity of osteoclasts, which are the main target of ODX in vicious cycle of bone metastases). (d) S-P1NP, percent change from baseline at week 12. Green, yellow and blue bars denote ODX 3.0 mg/kg, ODX 6 mg/kg and ODX 9.0 mg/kg, respectively. Values over 100 were truncated. *BSI values with increase >0.3 units, indicating progressive disease according to EXINI defined criteria.

received, and progressed on, 2–3 previous treatments with modern CRPC drugs (one patient with docetaxel, abiraterone, and Radium-223-dichloride; one with docetaxel, cabazitaxel, and abiraterone; one with docetaxel and abiraterone; one with docetaxel and enzalutamide; data not shown).

FAS data for B-ALP, S-P1NP, S-CTX and BSI, showing change from baseline at each time point sampled, were 36/54 (67%), 43/54 (80%), 44/54 (81%) and 15/41 (37%), respectively (Data for each arm are presented in Online Supplement Table S4).

The median time to progression (mTTP) of B-ALP, S-P1NP and S-PSA are summarised in Table 2. mTTP of metastases in bone, assessed 2 weeks after the last dose (maximum doses: 10): 19.7 weeks, no statistically significant differences between study arms. mTTP of soft tissue metastases, assessed 2 weeks after the last dose (maximum doses: 10): 21.6 weeks, no statistically significant differences between study arms.

Pain was assessed with the FACT-P instrument and overall health with EQ-5D. The data at 12 weeks demonstrated that 5/34 (14.7%) patients improved during treatment period with respect to pain, without escalating their World Health Organisation ladder pain medication (non-opioids to opioids). QoL according to EQ-5D questionnaire item "'your health today' demonstrated that 5/37 (13.5%) patients experienced improvement during treatment period. There were no statistically significant differences between study arms (data not shown). No bone flare was seen using PCWG3 criteria.

### 3.3. Safety

ODX was well tolerated. AEs interpreted as ODX related were recorded in 12 patients (21.8%). Fatigue, nausea, spinal pain and anaemia were noted as ODX AEs. However, only nausea and possibly fatigue appear to be ODX related. No disturbances in serum minerals (calcium, magnesium and phosphate) were recorded, and there was no drug-related nephrotoxicity. The majority of AEs were grades 1–2. No drug-related SAEs were seen. No statistically significant differences between study arms in terms of AEs, SAEs and CTCAE grades (Online Supplement Table S1 and Table S2).

## 4. Discussion

CRPC is the deadly form of PC. The metastatic cascade initially takes place in bone, thereafter at more distant sites [21]. Bone metastases are the main cause of death [4]. A bone-focused radionuclide treatment can curb disease progression and prolong OS [11,15]. The rationale behind the development of ODX is to effectively treat bone metastases with a novel mode of action. It binds via its

Table 2
Efficacy summary from maximum ten ODX treatment cycles.

| Efficacy measure | Statistic | 3.0 mg/kg ODX | 6.0 mg/kg ODX | 9.0 mg/kg ODX | Total |
|---|---|---|---|---|---|
| B-ALP: Relative change from baseline at 12 weeks for responders. | Median (95% CI) | −37.3 (−53.6, −29.9) [n = 6/15 (40%)][a] | −13.8 (−41.0, −6.2) [n = 8/12 (67%)][a] | −42.9 (−61.8, −6.3) [n = 5/12 (42%)][a] | −30.4 (−42.9, −11.8) [n = 19/39 (49%)][a] |
| S−P1NP: Relative change from baseline at 12 weeks for responders. | Median (95% CI) | −50.8 (−71.0, −22.3) [n = 8/15 (53%)][a] | −40.2 (−60.8, −7.1) [n = 8/12 (67%)][a] | −63.6 (−79.3, −33.3) [n = 4/12 (33%)][a] | −47.9 (−67.3, −34.0) [n = 20/39 (51%)][a] |
| S-CTX: Relative change from baseline at 12 weeks for responders. | Median (95% CI) | −75.4 (−93.0, −57.4) [n = 13/15 (87%)][a] | −87.0 (−93.4, −15.7) [n = 8/12 (67%)][a] | −91.2 (−98.3, −19.0) [n = 7/12 (58%)][a] | −82.4 (−93.0, −63.8) [n = 28/39 (72%)][a] |
| S-Osteocalcin: Relative change from baseline at 12 weeks for responders. | Median (95% CI) | −51.7 (−59.5, −24.1) [n = 12/15 (80%)][a] | −42.4 (−56.3,-20.0) [n = 7/12 (58%)][a] | −35.7 (−52.2,-15.4) [n = 5/12 (42%)][a] | −45.3 (−52.2,-27.8) [n = 24/39 (62%)][a] |
| BSI: Relative change from baseline at 12 weeks for responders. | Median (95% CI) | −27.6 (−70.5,-17.8) [n = 3/12 (25%)][a] | −9.8 (−44.1, −1.6) [n = 6/12 (50%)][a] | −27.2 (−54.9, −7.4) [n = 3/9 (33%)][a] | −15.0 (−44.1, −7.4) [n = 12/33 (36%)][a,b] |
| PFS, assessed at 2 weeks after last ODX dose. | Median, weeks (95% CI) | 20 (11.1, 22.3) | 22 (12.0, NA) | - (10.9, NA) | 22 (12.3, NA) |
| OS, assessed at 2 years after last ODX dose. | Median, weeks (95% CI) | - (62.9, NA) | 47 (20.3, 87.9) | 102 (18.4, NA) | 87 (57.0, NA) |
| TTP PSA, assessed at 2 weeks after last ODX dose. | Median, weeks (95% CI) | 12.3 (12.0, 12.6) | 12.1 (7.1, NA) | 12.4 (8.0, 14.1) | 12.3 (12.1, 12.4) |
| TTP B-ALP, assessed at 2 weeks after last ODX dose. | Median, weeks (95% CI) | 14.1 (10.1, NA) | 12.4 (7.9, NA) | 14.1 (8.1, NA) | 14.1 (12.1, NA) |
| TTP S-P1NP, assessed at 2 weeks after last ODX dose. | Median, weeks (95% CI) | - (7.9, NA) | 12.4 (6.1, NA) | 14.1 (7.0, NA) | 14.1 (12.0, NA) |
| TTP bone, assessed at 2 weeks after last ODX dose. | Median, weeks (95% CI) | 13.1 (11.3, NA) | 19.7 (11.9, NA) | - (12.3, NA) | 19.7 (12.3, NA) |
| TTP soft tissue, assessed at 2 weeks after last ODX dose. | Median, weeks (95% CI) | 20.0 (11.1, 22.3) | 21.6 (12.0, NA) | - (10.9, NA) | 21.6 (12.3, NA) |

B-ALP, bone alkaline phosphatase; BSI, bone scan index; bone, bone metastasis; CI, confidence interval, 95% CI is calculated for relative change from baseline median without distribution assumption; NA, not available; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; S-CTX, serum C-terminal telopeptide; S-P1NP, serum-aminoterminal-propeptide of Type I procollagen; soft tissue, soft tissue metastasis; TTP, time to progression.
Definition: time to progression of PSA, B-ALP and P1NP were defined as ≥25% increase from baseline at ≥12 weeks from baseline (in patients with no decline from baseline) or ≥25% increase above the nadir value, which was confirmed by a second value 3 or more weeks later (in patients with an initial decline from baseline). TTP in bone and TTP in soft tissue are defined according to PCCTWG3 [Scher HI, Morris MJ, Stadler WM *et al.* PCCTWG3 J Clin Oncol. 2016; 34(12):1402−18] and RECIST [Eisenhauer EA, Therasse P, Bogaerts J *et al.* Eur J Cancer. 2009; 45(2):228−247], respectively.
[a] Number of responders.
[b] BSI was performed in 35 of 54 patients at week 12. Two of the patients had investigations that were not evaluable, resulting in a total of 33.

alendronate moiety to hydroxyapatite exposed in bone metastases and exerts its cytotoxic activity via its guanidine moiety [13]. ODX was well tolerated and showed a benign safety profile. Treatment response with inhibition of the vicious cycle was supported by the pronounced reduction in CTX. The reduction in B-ALP, S-P1NP and S-Osteocalcin is in line with a secondary effect to the reduced osteoclast and tumour cell activities. The reduction in bone marker levels is in the same range as those seen after Radium-223-dichloride in symptomatic mCRPC [15] and asymptomatic mCRPC patients [22]. The ODX study was conducted during a period before BPAs were commonly recommended as part of the standard treatment of mCRPC [6–10]. The use of BPAs, 4 w before, and throughout, the treatment period, was an exclusion criterion. Despite this, an ODX-induced decrease in key bone marker levels was in the same range as that typically seen with zoledronate/denosumab [7,23]. The reduction in BSI, reflecting decreased metastatic burden as soon as after 12 weeks of treatment, is encouraging and at least on a par with data published for docetaxel, abiraterone and enzalutamide [24–26]. Reduction in bone markers and BSI was seen in all three dose arms, even in patients who had progressed on one or more lines of modern CRPC drugs. Analogous to treatment with Radium-223-dichloride, another inhibitor of the vicious cycle in bone metastases, only some effect was seen on PSA response. This could, as in the case of Radium-223-dichloride, possibly be explained by a major effect on AR-negative, poor PSA-producing, PC cells, which are abundantly present in the aggressive form of CRPC bone metastases [27,28]. The main purpose of this study was also to document safety and tolerability (regarding the rationale behind dose selection, see Online Supplement, 'Selection of Doses'). All doses were well tolerated and demonstrated a benign safety profile. No jaw osteonecrosis was reported. There were no statistical differences between study arms regarding the efficacy parameters. This is not quite unexpected because even the lower doses should be sufficient to 'saturate' the hydroxyapatite residues exposed in bone metastases.

The study has a number of limitations: It was not placebo controlled, and the non-completion rate during treatment period was high. Although the size was sufficient for the assessment of safety and tolerability, the trial was not powered to detect small differences in efficacy. The trial was prematurely discontinued due to too low a recruitment rate towards the end. This is a limitation, although it is unlikely that the expected recruitment to the 9 mg/kg arm would have changed the overall results and conclusions. Radiology and laboratory assessments were not done from the time point 2 weeks after the last ODX dose, limiting the assessment of PFS. Although the study arms were relatively well balanced at study start, differences in prognostic factors may explain the differences in OS data. Responders to ODX seemed to benefit with longer OS than non-responders, a finding that, however, has to be interpreted with caution (Online Supplement Fig. S3).

Among the strengths is the broad inclusion criteria used, allowing treatment-naïve, as well as heavily pretreated, CRPC patients to participate. This fact gave us the opportunity to verify the efficacy and benign safety profile independently of previous CRPC therapies and metastatic burden. Another strength is the utilisation of BSI, verifying the reduction of bone metastatic burden already after 12 weeks.

## 5. Conclusion

ODX is a novel cytotoxic drug candidate that, through its alendronate moiety, targets osteoclasts in bone metastases and inhibits the vicious cycle. The decrease, especially in CTX, reflects its mode of action. Although used in a predetermined limited number of cycles, it proved active at all three doses and in the vast majority of cases. BSI demonstrated decreased bone metastatic burden. ODX was effective in CRPC treatment-naïve, as well as heavily pretreated patients.

## Ethics committee approval

The study was conducted in accordance with Declaration of Helsinki (2008 version), Good Clinical Practice (CPMP/ICH/135/95), and the EU Directive 2001/20/EC. Approval was obtained from institutional review boards and ethical committees at all study centres prior to study start. Written informed consent was obtained from all subjects prior to participation.

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## Authors' contributions

A.R., S.N., and C.T.-K. designed the study and prepared the protocol. C.T.-K., E.V., M.K., T.T., K.O., U.N., C.N., S.-O.A., O.H., and M.M.-H. collected the data. C.T.-K. acted as principal investigator. A.R.H. was the study coordinator. C.T.-K., S.N., C.T.-K., S.N., and A.R.H. wrote the article. All authors were involved in the critical review of the article and approved the final version.

## Contract research organisations

Crown CRO oy, Espoo, Finland (Monitoring, Pharmacovigilance and Medical Writing of CSR).

StatFinn, Espoo, Finland (Statistics & Data Management).

## Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Anders Holmberg is employee, board member, and shareholder of Dextech Medical. Sten Nilsson is board member and shareholder of Dextech Medical. All other co-authors (Thellenberg-Karlsson, E Vjaters, M Kase, T Tammela, K Ojamaa, C Nyman, U Norming, S-O Andersson, O Hublarov, M Marquez-Holmberg, E Castellanos, A Ullén) have no conflicts of interest to declare.

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## Appendix A. Supplementary data

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