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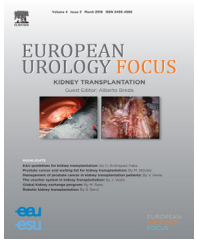

Prostate Cancer

Liproca Depot: A New Antiandrogen Treatment for Active Surveillance Patients

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Abstract

Background: There is increasing interest in nonmorbid treatments for low- and intermediate-risk prostate cancer with fewer side effects than surgery or radiotherapy.
Objective: To investigate the tolerability, safety, and antitumor effects of the intraprostatic NanoZolid depot formulation Liproca Depot (LIDDS AB, Uppsala, Sweden) with antiandrogen 2-hydroxyflutamide (2-HOF) in men with low- or intermediate-risk localized prostate cancer managed with active surveillance.
Design, setting, and participants: This clinical phase 2b trial, LPC-004, involved 61 patients. The 2-HOF-containing formulation Liproca Depot was injected transrectally into the prostate under ultrasound guidance. A single dose of 35% or 45% of the prostate volume (study part 1) and a fixed dose of 16 or 20 ml (study part 2) of the formulation were evaluated.
Outcome measurements and statistical analyses: The primary endpoints were tolerability and the reduction in serum prostate-specific antigen (PSA) 5 mo after injection. Antitumor effects were evaluated with magnetic resonance imaging (MRI) and prostate biopsies. Quality of life was assessed using a validated questionnaire (International Prostate Symptom Score).
Results and limitations: All doses were safe and well tolerated, without hormonal side effects. In part 2 of the study, the PSA reduction was greatest for the group receiving 16 ml, with an average decrease of 14%, and 95% of patients had a PSA reduction. Some 78% of patients showed a prostate volume decrease compared to baseline. Prostate MRI and biopsies confirmed stable or reduced lesion size. However, post treatment biopsies were performed at the discretion of the investigator, and not routinely. Most patients were amenable to a second injection.
Conclusions: PSA and prostate volume decreased in most patients. Indications of efficacy were shown by post-treatment MRI and biopsies demonstrating stabilization or regression in the majority of cases.

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Patient summary: Liproca Depot is a safe, minimally invasive treatment that offers the potential for cancer control in patients with intermediate-risk prostate cancer. Further clinical evaluation is warranted.

1. Introduction

Active surveillance is a strategy involving close monitoring of patients with low- or intermediate-risk prostate cancer. A risk with active surveillance is undertreatment of occult clinically significant disease. Approximately 40% of the patients initiating a no-treatment approach undergo definitive therapy within 10 yr, usually because of upgrading of cancer on subsequent biopsies [1–3]. Approximately 25% of men diagnosed with Gleason grade group 1 cancer (indolent and non-metastasizing) according to systematic biopsies harbor higher-grade cancer elsewhere in the prostate [4,5]. Grade group 1 lesions may also progress to a more aggressive phenotype. This occurs at a transition frequency of 1.5–2.3% per year, or 15–20% by 10 yr [6]. Most Gleason grade 4 and 5 cancers harbor molecular alterations that are characteristic of high-grade cancer [7]. For intermediate-risk patients (grade group 2–3 or prostate-specific antigen [PSA] >10 ng/ml) on active surveillance, approximately half show progression after 5 yr [8–10]. Consequently, prostate cancer patients on active surveillance are followed for an extended period of time, during which they are periodically rebiopsied. A no-treatment approach also includes the psychological burden of carrying a known untreated cancer.

Therefore, there is increasing interest in nonmorbid treatments for low- and intermediate-risk prostate cancer with fewer side effects than surgery or radiotherapy as alternatives to active surveillance. The aim of this approach is to delay or halt disease progression and reduce the need for surgery or radiotherapy. Drugs developed for advanced and metastasized prostate cancer (eg, enzalutamide, apalutamide, bicalutamide) may play a role in early disease, but the systemic adverse effects associated with these drugs limit their appeal [11].

Liproca Depot (LIDDS AB, Uppsala, Sweden) is an intraprostatic injection of the antiandrogen 2-hydroxyflutamide (2-HOF) in a calcium sulfate–based depot produced with the NanoZolid (LIDDS AB) drug delivery platform, for which the antiandrogen is slowly released over a period of up to 6 mo [12,13]. Treatment with Liproca Depot is a focal therapy that can be performed in an outpatient urology clinic with local anesthesia and a transrectal procedure similar to prostate biopsy.

2. Patients and methods

2.1. Drug product

The product consists of a powder with 33 wt.% 2-HOF in calcium sulfate, and an aqueous solution with 0.25 wt.% sodium carboxymethyl cellulose. Immediately before administration, the components are mixed to a viscous suspension with a 2-HOF concentration of 0.23 g/ml.

2.2. Study design

Clinical trial LPC-004 was a single-blind, two-stage, dose-finding, randomized, single dose, multicentre, phase 2b study (EudraCT No 2016-002504-43, NCT03348527) performed at ten urology centers in Finland, Canada, and Lithuania. Patients included in the study were men aged 18–80 yr diagnosed with localized prostate cancer assigned to active surveillance with a Gleason score of 3 + 3 or 3 + 4 and PSA $\leq$ 20 ng/ml. The primary endpoints were tolerability and the PSA reduction at 5 mo after injection. The efficacy of Liproca Depot was assessed in terms of changes in PSA, prostate volume (PV), Prostate Imaging-Reporting and Data System (PI-RADS) score, and prostate biopsy histology.

Part 1 of the study included 20 patients and focused on the safety and tolerability of high doses of Liproca Depot. The patients received the suspension under local anesthesia; using a transrectal ultrasound probe for guidance, Liproca Depot was injected through a 17-gauge needle at a dose corresponding to either 35% or 45% of their PV. In part 1, 5–24 ml (1150–5520 mg of 2-HOF) was distributed equally between both prostate lobes (both sides of the urethra). In part 2, 41 patients received a fixed dose of 16 or 20 ml (3680 or 4600 mg of 2-HOF) injected in proximity to the lesions, with a weight for a higher injection volume distributed in the lobe with more lesions (where there was a difference), as identified by magnetic resonance imaging (MRI; Table 1).

2.3. PSA, pharmacokinetics, and testosterone

Blood samples for pharmacokinetic (PK) analysis of 2-HOF were collected from 37 patients in study parts 1 and 2, representing at least seven patients from each of the four treatment groups. PSA and testosterone were measured in all patients. PSA responders were defined as patients showing a PSA reduction of more than 15%, thus exceeding the expected normal variations [14,15]. Serum samples were analyzed for PSA and testosterone using a chemiluminescence assay and for 2-HOF via liquid chromatography tandem mass spectrometry.

2.4. Magnetic resonance imaging

PV and PI-RADS version 2.0 scores were measured via MRI at screening or performed within 12 mo before screening and at month 5 after injection. MRI was used for lesion identification and planning of volume distribution in the prostate lobes. Measurements were performed with 3-T clinical scanners using whole-body coils as both the excitation and receiver phase-array coils. MRI examinations using the standard clinical protocol according to the European Society of Urogenital Radiology included axial T1-weighted, axial, coronal, and sagittal T2-weighted, and diffusion-weighted imaging (DWI) sequences including the apparent diffusion coefficient (ADC). MRI for PI-RADS score evaluation was performed by two radiologists experienced in uro-oncological imaging.

2.5. Histopathology

Transrectal ultrasound-guided prostate biopsies were taken at screening for all patients. Pathology response was not the primary endpoint, and therefore post-treatment biopsies were not performed routinely. Biopsies were performed at month 6 (study end) for a subset of patients (n = 6).

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Table 1 – Baseline characteristics and doses by treatment group[a]

	Part 1		Part 2	
	Treatment group 1	Treatment group 2	Treatment group 3	Treatment group 4
Treatment details				
Volume strategy	35% of PV	45% of PV	Fixed volume	Fixed volume
Liproca Depot (ml)	5–20	8–24	16	20
2-HOF (mg)	1150–4600	1840–5520	3680	4600
Patients (*n*)	10	10	21	20
PSA (ng/ml)	8.2 ± 3.3	8.5 ± 3.3	8.7 ± 4.2	6.7 ± 3.4
PV (ml)	35.0 ± 12.8	39.8 ± 10.9	34.7 ± 13.0	38.1 ± 10.0
PI-RADS, *n* (%)				
≤3	4 (44)	8 (80)	6 (29)	7 (35)
4	5 (56)	1 (10)	8 (38)	11 (55)
5	0 (0)	1 (10)	7 (33)	2 (10)
D'Amico risk group, *n* (%)				
Low risk	6 (60)	7 (70)	14 (67)	10 (50)
Intermediate risk	4 (40)	3 (30)	7 (33)	10 (50)
Age (yr)	63.4 ± 8.3	63.3 ± 4.3	65.4 ± 7.0	62.0 ± 6.0

2-HOF = 2-hydroxyflutamide; PI-RADS = Prostate Imaging-Reporting and Data System; PSA = prostate-specific antigen; PV = prostate volume.
[a] Data for continuous variables are presented as mean ± standard deviation.

2.6. Quality of life

Quality of life was evaluated using the validated International Prostate Symptom Score (IPSS) questionnaire. To simplify study implementation, a hormonal-specific questionnaire was not used.

2.7. Statistical analysis

The primary efficacy endpoint, PSA reduction from baseline at month 5, was analyzed using a one-sided paired *t* test or a nonparametric one-sided Wilcoxon matched-paired sign-rank test. Statistical testing was performed at a one-sided significance level of 0.05. The corresponding secondary efficacy endpoint, percent PSA change from baseline over time, was analyzed using a two-sided paired *t* test or a nonparametric two-sided Wilcoxon matched-paired sign-rank test. Statistical testing was performed at a two-sided significance level of 0.05. Other secondary endpoints are summarized and presented in a descriptive manner.

2.8. Ethical approvals

LPC-004 was approved by the ethics committee or institutional review board at each hospital and by the national medical products agencies in Finland, Canada, and Lithuania. All patients signed informed consent forms before receiving treatment.

3. Results

3.1. Large-volume tolerance

In part 1, injections of up to 24 ml of Liproca Depot, corresponding to 45% of PV, were used. Transient urinary retention was the most common adverse event (AE) in both treatment groups 1 and 2 (Table 2). This resolved spontaneously in all patients within 1–29 d, and no patient required intervention beyond a catheter. Symptoms of prostatitis developed in six patients (10%). There were no deaths or withdrawals due to AEs during the study.

3.2. PSA reduction and percent change

In part 1 of the study, 55% of the patients experienced a PSA reduction during the study. The greatest percent PSA reduction from baseline in part 1 was seen in treatment group 2 (dose 45%) with 54% at week 2. In part 1, the mean PSA change was not statistically significant.

In part 2, several patients in both the 16 and 20 ml dose groups showed a PSA response (>15% PSA reduction) lasting for the study duration of 6 mo (Fig. 1). The 16 ml dose

Table 2 – Any AEs (grades 1–5, of which 3 is severe) and number of SAEs reported

	Part 1				Part 2				All (*n* = 61)	
	TG 1 (*n* = 10)		TG 2 (*n* = 10)		TG 3 (*n* = 21)		TG 4 (*n* = 20)		All AEs	SAEs
	All AEs	SAEs	All AEs	SAEs	All AEs	SAEs	All AEs	SAEs		
Any AE	16	4 (2)	19	1 (0)	58	0 (1)	57	3 (3*)	150	8 (6*)
Most common treatment-related AEs										
Dysuria	1	0	2	0	8	0	7	0	18	0
Hematuria	0	0	0	0	5	0	5	0	10	0
Urinary retention	3	2	1	1	3	0	5	0	12	3 (0)
Prostatitis	0	0	0	0	2	0	4	2 (2)	6	2 (2)

AE = adverse event; SAE = severe AE; TG = treatment group.
* Of which one was sepsis, a grade 4 (life-threatening) AE.

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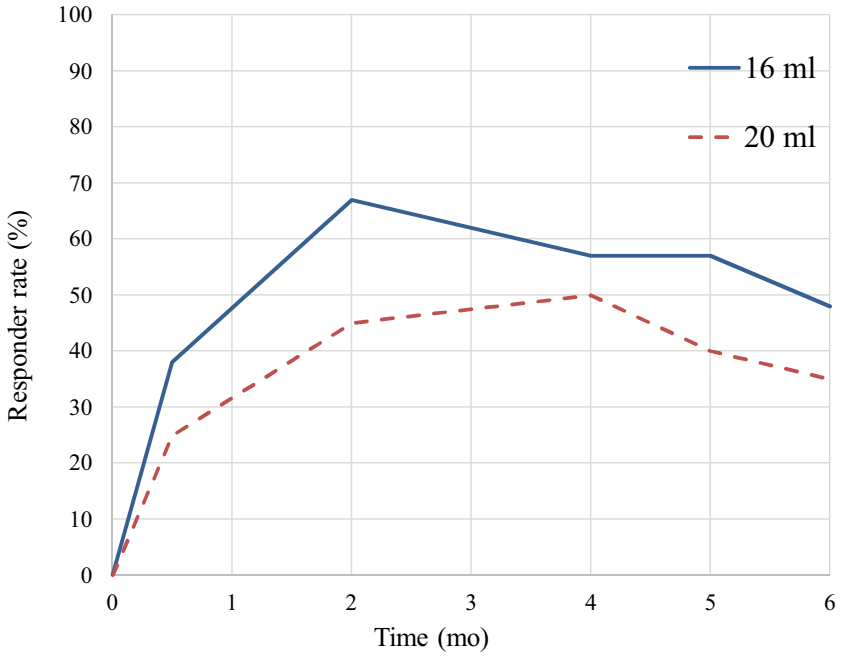

Fig. 1 – Rate of responders (proportion of patients showing more than 15% prostate-specific antigen reduction) in LPC-004 study part 2.

induced a greater PSA reduction, with a responder rate of 67% at the time point for maximum response (2 mo), compared to 50% for the 20 ml dose (4 mo). PSA responder rates at month 5 were 57% in the 16 ml group and 40% in the 20 ml group. The mean percent reduction at month 5 was 14% in the 16 ml group ($p < 0.05$). This difference in PSA change from baseline between the 16 and 20 ml groups was more pronounced at month 2 (Fig. 2A) than at month 5 (time point for the primary endpoint; Fig. 2B). There was also a greater percent change in PSA from baseline for the 16 ml group than for the 20 ml group at both month 2 (Fig. 2A) and 5 (Fig. 2B). The individual variations in percent PSA change were substantial, ranging from −55% to +25% for the 16 ml group and from −36% to +216% for the 20 ml group at month 5 (Fig. 2B).

A few patients show a very high but transient PSA increase. This affected the mean PSA values strongly, particularly for men receiving the 20 ml dose. The patient whose PSA increased 216% (Fig. 2B) also reported prostatitis, which is likely to explain his dramatic PSA rise.

3.3. PK data

The initial 2-HOF boost release was rapid and was not related to injected volume in the majority of the patients. All PK parameters exhibited high interpatient variability. The average maximum concentration (C_{max}) was 1780 ng/ml and ranged from 139 to 9850 ng/ml (coefficient of variation [CoV] 145%). After initial release of 2-HOF, plasma concentrations decreased rapidly to levels well below 1000 ng/ml. The average area under the plasma concentration-time curve was approximately 5000 ng·d/ml (CoV 80.3%) from time zero to the last quantifiable concentration, and 6120 ng·d/ml (CoV 73.3%) from time zero to infinity. The average 2-HOF plasma concentration over time in the four treatment groups is presented in Figure 3.

3.4. Testosterone

There was a nonsignificant ($p > 0.05$) increase in mean serum testosterone at month 2 (an increase of 1–2 nmol/l). However, a small but statistically significant ($p = 0.04$) change in serum testosterone was seen in treatment group 2 (3.4 nmol/l), probably reflecting a transient effect of flutamide on the pituitary-gonadal axis. At month 6, the testosterone levels had returned to baseline levels.

3.5. Prostate volume

In parts 1 and 2, 75% and 78% of the patients, respectively, showed a decrease in PV at month 5. The median PV change was −9% for the 16 ml group and −12% for the 20 ml group, Among the patients with a decrease in PV, the range was from −4% to −24% in the 16 ml group and −3% to −38% in the 20 ml group (Table 3 and Fig. 4).

3.6. MRI evaluation

At screening, most patients had MRI findings with a PI-RADS score of 3 or 4. For parts 1 and 2 of the study, one and nine patients, respectively, presented with a PI-RADS 5 lesion at diagnosis. In two patients, a suspected new lesion was detected at month 5 (both were PI-RADS 3). Figure 5 shows an MRI series example for a patient experiencing a decrease in PI-RADS score at month 5.

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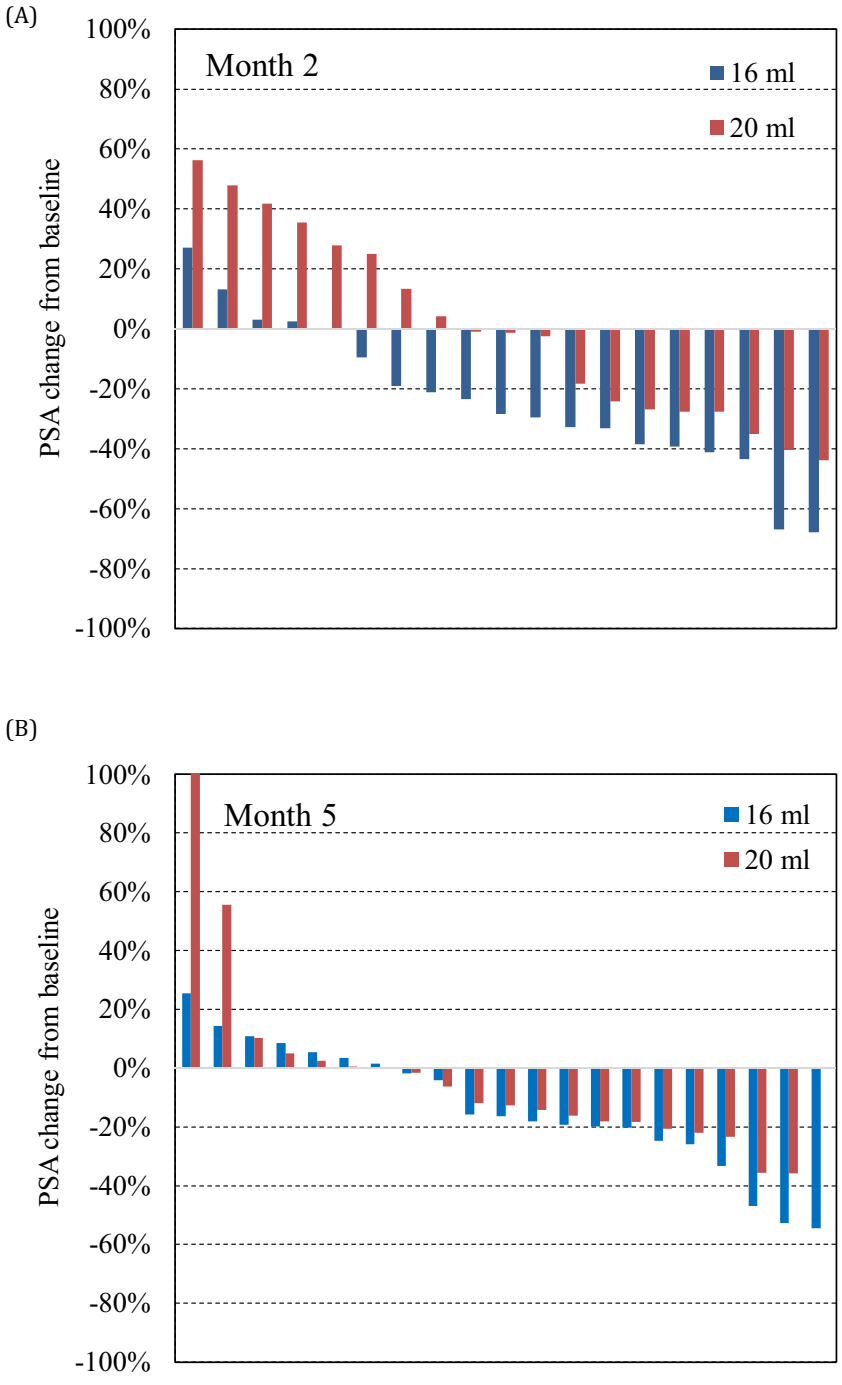

Fig. 2 – Individual prostate-specific antigen (PSA) reductions relative to baseline at (A) month 2 and (B) month 5 in LPC-004 study part 2.

No worsening of MRI PI-RADS score was seen in any patient. Interestingly, a one-step decrease in PI-RADS score was seen in nine patients: two patients in part 1 (10%; from 4 to 3) and seven patients in part 2 (17%; from 5 to 4 [three patients] or from 4 to 3 [four patients]).

3.7. *Adverse events*

The majority of AEs were mild or moderate. There were very few ($n = 8$) severe AEs (Table 2). The most common AEs were dysuria, hematuria, urinary retention, and prostatitis. The reactions were mainly judged to be related to the injection procedure. No patient experienced any of the side effects commonly associated with systemic antiandrogen monotherapy (loss of libido, sarcopenia, and gynecomastia). Six serious AEs (SAEs) were reported in five patients (two in the same patient). Five SAEs were judged to be treatment-related, all infections which developed shortly after the injection. All SAEs resolved with systemic antibiotic treatment without sequelae.

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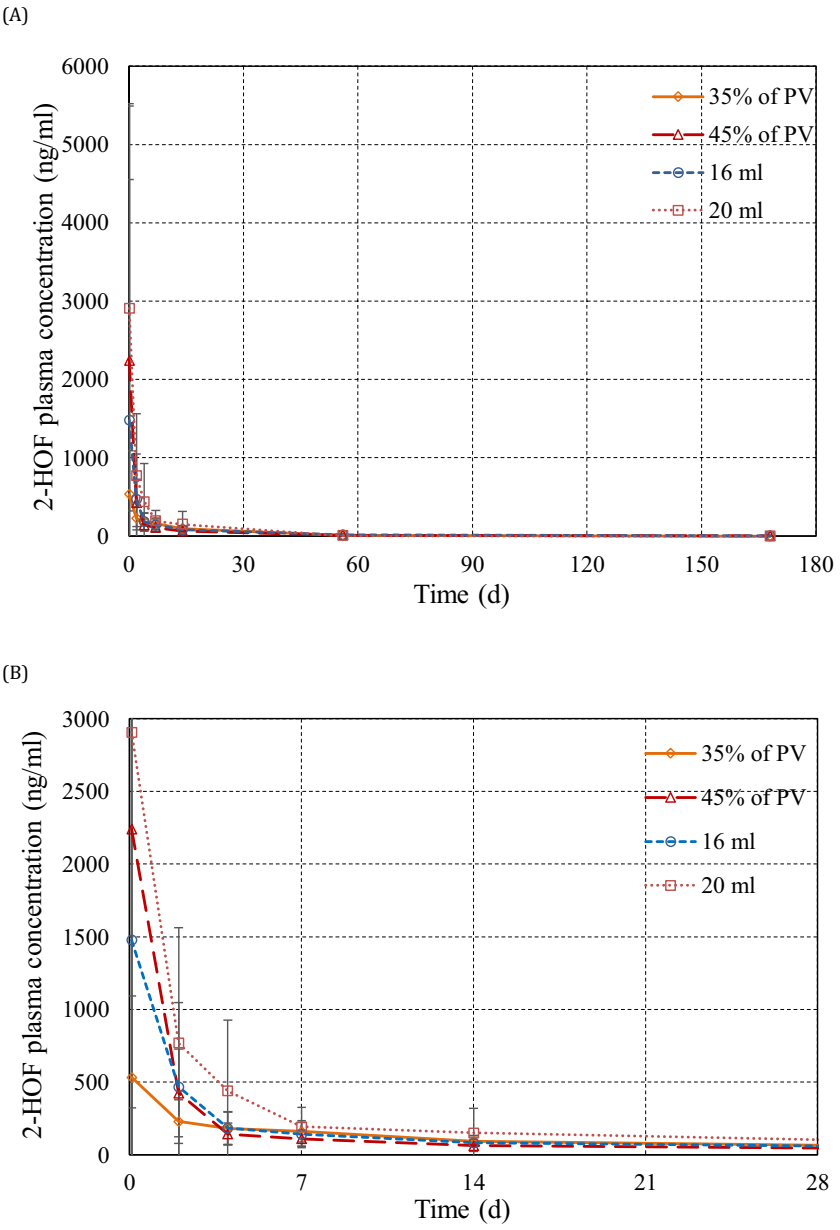

Fig. 3 – Average 2-hydroxyflutamide (2-HOF) plasma concentration versus time for each treatment group including (A) all concentrations for the duration of the study and (B) truncated at 3000 ng/ml and 28 d.
PV = prostate volume.

Table 3 – Mean and median PV changes for parts 1 and 2 of clinical trial LPC-004

	Part 1			Part 2		
	TG 1	TG 2	All	TG 3	TG 4	All
Patients (*n*)	10	10	20	21	20	41
PV change at month 5(%)						
Mean	−3	−16	−10	−7	−9	−8
Median	−4	−15	−12	−9	−12	−9
Range	−28 to +39	−36 to −4	−36 to +39	−24 to +13	−38 to +72	−38 to +72
Patients with PV decrease (%)	50	100	**75**	71	85	**78**

PV = prostate volume; TG = treatment group.

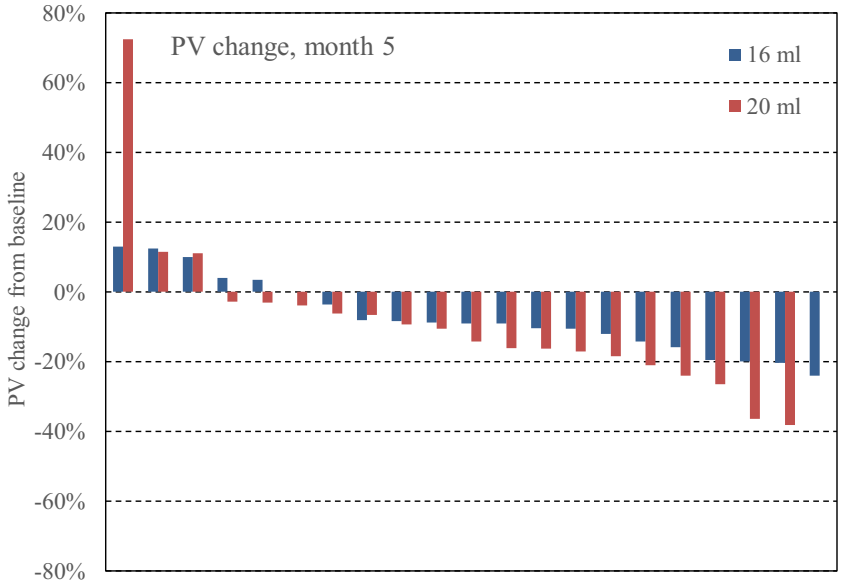

Fig. 4 – Individual prostate volume (PV) changes relative to baseline after 5 mo in LPC-004 study part 2.

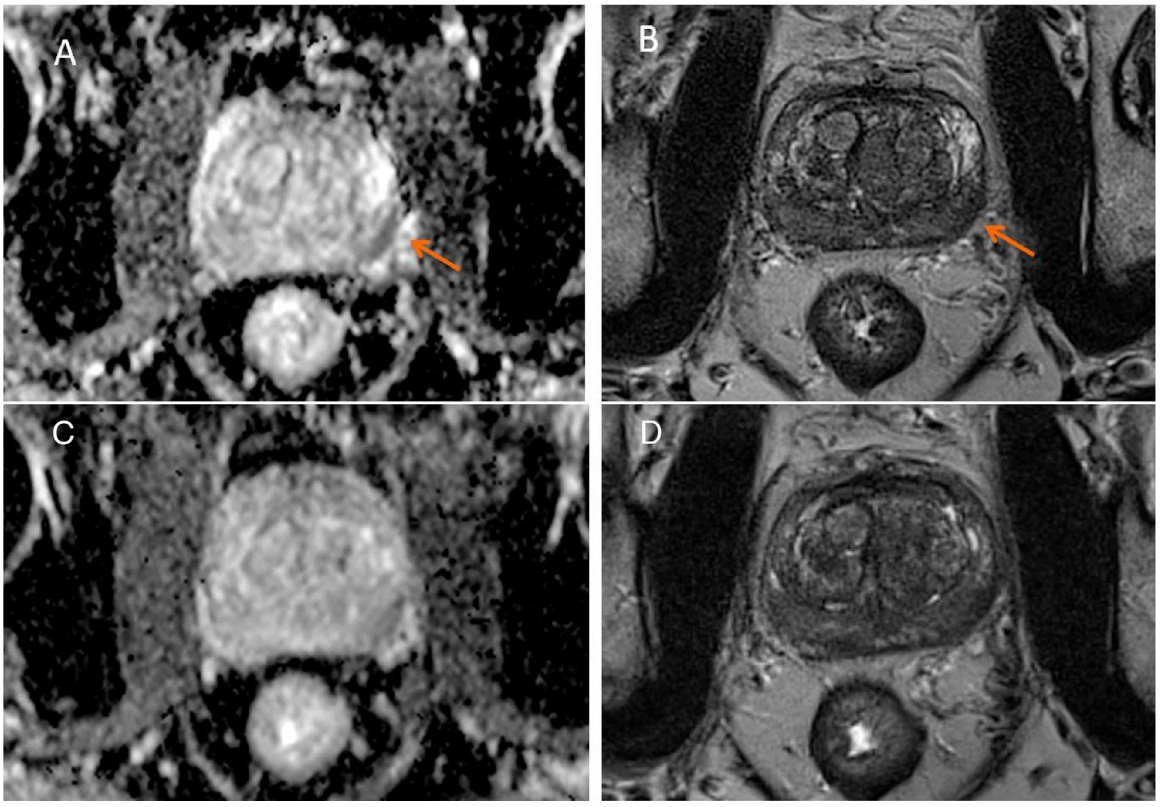

Fig. 5 – Imaging for a patient with a Gleason 3 + 4 tumor in the left peripheral zone. (A,B) Magnetic resonance imaging at screening and (C,D) at a follow-up visit 5 mo after local treatment with 16 ml of Liproca Depot. (A) Transaxial apparent diffusion coefficient (ADC) map and (B) transaxial T2-weighted image (T2WI) in the same mid-zone level shows a 1.9-cm tumor in the left peripheral zone (Prostate Imaging-Reporting and Data System score 5, orange arrow). (C) ADC map and (D) T2WI showing a decrease in tumor size to 1.1 cm and less demarcation on the ADC map.

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3.8. Histopathology

End-of-study biopsies were taken in a total of six patients at the discretion of the investigator. The biopsies showed persistent Gleason grade group 1 cancer in five patients and a decrease in Gleason grade group from 2 to 1 in one patient.

3.9. Quality-of-life data

Prostate symptoms, assessed using the IPSS, slightly worsened during the first few weeks following injection of Liproca Depot. There were no significant changes from baseline after the 2-wk post-treatment assessment. At 2 mo after treatment, 70% of the patients in part 1 and 83% of the patients in part 2 were amenable to a second injection of Liproca Depot.

4. Discussion

Liproca Depot was safe and well tolerated. The AE pattern did not clearly identify a tolerability threshold, as the total number of AEs reported was similar between the 16 (59 AEs) and 20 ml (57 AEs) groups (Table 2). However, SAEs (n = 3) occurred for the larger injection volume group (20 ml) in part 2.

The changes in PSA and PV were quite variable. Other conditions may influence PSA levels. One patient experienced a dramatic PSA increase concomitant to acute prostatitis. However, most patients experienced progressive reductions in PSA and PV over 6 mo. Liproca Depot was well tolerated, even at large volumes. It is plausible that still larger injection volumes could be administered to men with larger PV.

In vitro studies of the NanoZolid technology have demonstrated a multiphase release profile of 2-HOF with Liproca Depot [13,16] involving an initial boost followed by slower sustained release. The in vivo release profile is also affected by variations in the vascularization and tissue characteristics of the gland, as well as vascular alteration induced by the injection procedure. For the majority of patients (70%), C_{max} was reached at the first observation of 2 h, while for the remaining patients C_{max} was detected after 1–14 d.

For each of the four patient groups in LPC-004, there were two or three patients with transient C_{max} levels exceeding the steady-state levels observed for oral flutamide, specified as between 1556 and 2284 ng/ml [17]. However, a short period of high plasma concentrations followed by long-term negligible concentration is likely to be associated with little or no risk of side effects related to androgen deprivation. No such side effects were seen in the patients with high initial plasma 2-HOF concentrations.

The median elimination half-life ($t_{1/2}$) was estimated to be 12 (2.6–67) d, suggesting absorption-limited kinetics for 2-HOF because of its slow release from Liproca Depot. The steady-state $t_{1/2}$ of 2-HOF is 8–10 h [18].

Testosterone levels in plasma remained unaffected, showing that the low systemic exposure to 2-HOF from Liproca Depot over time did not significantly alter the gonadal-pituitary axis. Similar results were seen in a previous Liproca Depot study [12].

MRI revealed no progression of any lesions present at baseline following intraprostatic injection of Liproca Depot. In part 2 of the study, seven of 41 patients (17%) showed a reduction in lesion PI-RADS score.

Liproca depot may effect cancer control by inducing apoptosis or by inhibiting cell growth through cell cycle arrest. Either mechanism may result in long-term suppression of cancer. If the mechanism is cell cycle arrest, persistent disease may still be seen on biopsy. We believe that the very low serum levels achieved by local prostatic administration would not be sufficient to induce anticancer effects.

The study has some limitations. This was a dose-finding phase 2b study with primary endpoints of safety and PSA response. The cohort size was modest, and a longer follow-up period would have been needed to be able to draw final conclusions about oncologic effectiveness. Post-treatment biopsies were performed at the discretion of the investigator, and not routinely. We acknowledge that routine post-treatment biopsies would have provided more robust evidence on oncologic efficacy. Although hormonal side effects were not observed, a hormonal-specific questionnaire would have strengthened the study.

The results presented should form the basis for studies on the efficacy of Liproca Depot for cancer control in patients with early-stage prostate cancer. A larger cohort with longer follow-up, (eg, with cancer progression as the primary objective) is required to validate these observations.

5. Conclusions

Intraprostatic injections of Liproca Depot at doses up to 24 ml (5520 mg of 2-HOF) were safe and well tolerated, with mild and transient adverse events. No hormonal reactions typically associated with systemic antiandrogen therapy were observed.

PSA and prostate volume decreased in most patients, consistent with the antiandrogen effect of the therapy. In part 2 of the study, the PSA response lasted for the full study duration of 6 months in 35–48% of patients. At month 5, 78% of the patients showed a PV decrease compared to baseline. MRI imaging revealed no progression over the study period.

The study results support a dose of 16 ml of Liproca Depot, corresponding to 3680 mg of 2-HOF, as an appropriate dosage for future studies. Further studies to determine the oncologic efficacy are warranted.

Author contributions: Stefan Grudén had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.
Acquisition of data: Gauffin, Grudén.
Analysis and interpretation of data: Klotz, Tammela, Bjartell, Grudén, Axén, Gauffin.
Drafting of the manuscript: Grudén.

Critical revision of the manuscript for important intellectual content: Klotz, Tammela, Richard, Bjartell, Grudén, Axén, Gauffin.
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