



Clinical trial results:

An open, single dose, antitumor effect study of 2-hydroxyflutamide as a controlled release product (Liproca® Depot), injected into the prostate in patients with localized prostate cancer.

Summary

EudraCT number	2011-001137-16
Trial protocol	SE FI
Global end of trial date	05 November 2015

Results information

Result version number	v1 (current)
This version publication date	03 June 2016
First version publication date	03 June 2016

Trial information

Trial identification

Sponsor protocol code	LPC-003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02341404
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LIDDS AB
Sponsor organisation address	Virdings allé 32b, Uppsala, Sweden, 75450
Public contact	Monica Wallter, LIDDS AB, 46 (0)737070922, monica.wallter@liddspharma.com
Scientific contact	Carl-Gustaf Gölander, LIDDS AB, 46 (0)761354354, carl-gustaf.golander@liddspharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 August 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize and to quantify the histopathological changes in the surgical specimens obtained in patients undergoing prostatectomy in addition to imaging changes (MRI) following a single injection of Liproca® Depot in patients with localized prostate cancer.

Protection of trial subjects:

Patients were observed in the clinics during the study visits. Physical examination and vital signs were taken at study start and end of study, while blood samples for Clinical Chemistry and hematology were taken at all visits. These safety lab data were continuously reviewed by PI for changes and abnormalities.

Background therapy:

None.

Evidence for comparator:

No comparator used.

Actual start date of recruitment	31 August 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 13
Country: Number of subjects enrolled	Finland: 10
Worldwide total number of subjects	23
EEA total number of subjects	23

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	10
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study contains two parts; Part I First Patient Visit 09 MAY 2012, Last Patient Visit 17 JUL 2013. After completion, an extension with Part II was done. Part II FPV 17 DEC 2014, LPV 18 MAY 2015. Two sites; Tampere University Hospital (Dept. of Surgery) and Uppsala University Hospital (Dept. of Urology) participated in both parts of the study.

Pre-assignment

Screening details:

The study population was men, between 50 and 75 years, with localized prostate cancer (T1c,T2a-c; Gleason score equal to, or less than, 3+4; PSA less than 20 ng/ml), verified by biopsy with no previous or on-going hormone therapy for prostate cancer. 18 pts were enrolled for Part I and 5 pts for Part II.

Part I: 600-2000 mg

Part II: 1800-2400 mg

Period 1

Period 1 title	Inclusion
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This study was an open, Phase IIa, non-randomized, multicentre study (2 sites).

Arms

Are arms mutually exclusive?	Yes
Arm title	Baseline (Part I- 15vol% Liproca per ml prostate)

Arm description:

Part I of the study, where the planned dose was 600-2000 mg 2-HOF and 6 weeks follow-up until prostatectomy.

Arm type	Experimental
Investigational medicinal product name	Liproca Depot
Investigational medicinal product code	
Other name	2-hydroxyflutamide (2-HOF)
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intraprostatic use

Dosage and administration details:

The formulation consists of two sterile Components, one aqueous liquid (Liproca Diluent) and a dry powder, containing the active drug pre-filled in a mixer container (Liproca Powder). The two components are, prior to injection, mixed under aseptic conditions to a paste, which will be transferred to a syringe, and administered with injection into the prostate.

For Part I, a dose of 600-2000 mg 2-HOF was planned as single dose (corresponding to 3-10 ml ready-mixed paste). When deciding the total and individual dose to be injected, the total prostate volume, number of foci and total tumour volume were taken into consideration in each patient. The individual dosing strategy was developed based on information from biopsies and imaging. Guideline was 1.5 ml of ready-mixed paste per 10 ml prostate volume, with a maximum amount of 10 ml prepared paste totally.

Local injection of ready-mixed paste, administered via rectum and with ultrasound guidance, in and around major tumour foci.

Arm title	Baseline (Part II - 30vol% Liproca per ml prostate))
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Arm description:

Part II of the study, where the planned dose was 1800-2400 mg 2-HOF and 8 weeks follow-up until prostatectomy.

Arm type	Experimental
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Investigational medicinal product name	Liproca Depot
Investigational medicinal product code	
Other name	2-hydroxyflutamide (2-HOF)
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intraprostatic use

Dosage and administration details:

The formulation consists of two sterile Components, one aqueous liquid (Liproca Diluent) and a dry powder, containing the active drug pre-filled in a mixer container (Liproca Powder). The two components are, prior to injection, mixed under asptic conditions to a paste, which will be transfered to a syringe, and administrated with injection into the prostate.

For Part II, the target dose of Liproca Depot was 1800-2400 mg corresponding to approximately 30% of the prostate volume. When deciding the individual dose to be injected, the total prostate volumem number of tumour foci and total tumour volume were taken into consideration in each patient. If tumour were found in both lobes, the distribution of paste shoule be related to the amount of tumour in each lobe.

Local injection of ready-mixed paste, administrated via rectum and with ultrasound guidance, in and around major tumour foci.

Number of subjects in period 1	Baseline (Part I- 15vol% Liproca per ml prostate)	Baseline (Part II - 30vol% Liproca per ml prostate))
Started	18	5
Completed	18	5

Period 2

Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)

Arm description:

Part I of the study, were the planned dose was 600-2000 mg 2-HOF and 6 weeks follow-up until prostatectomy.

Arm type	Experimental
Investigational medicinal product name	Liproca Depot
Investigational medicinal product code	
Other name	2-hydroxyflutamide (2-HOF)
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intraprostatic use

Dosage and administration details:

The formulation consists of two sterile Components, one aqueous liquid (Liproca Diluent) and a dry

powder, containing the active drug pre-filled in a mixer container (Liproca Powder). The two components are, prior to injection, mixed under aseptic conditions to a paste, which will be transferred to a syringe, and administered with injection into the prostate.

For Part I, a dose of 600-2000 mg 2-HOF was planned as single dose (corresponding to 3-10 ml ready-mixed paste). When deciding the total and individual dose to be injected, the total prostate volume, number of foci and total tumour volume were taken into consideration in each patient. The individual dosing strategy was developed based on information from biopsies and imaging. Guideline was 1.5 ml of ready-mixed paste per 10 ml prostate volume, with a maximum amount of 10 ml prepared paste totally.

Local injection of ready-mixed paste, administered via rectum and with ultrasound guidance, in and around major tumour foci.

Arm title	Treatment 8 weeks (Part II- 30vol% Liproca/ml prostate)
Arm description: Part II of the study, where the planned dose was 1800-2400 mg 2-HOF and 8 weeks follow-up until prostatectomy.	
Arm type	Experimental
Investigational medicinal product name	Liproca Depot
Investigational medicinal product code	
Other name	2-hydroxyflutamide (2-HOF)
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intraprostatic use

Dosage and administration details:

The formulation consists of two sterile Components, one aqueous liquid (Liproca Diluent) and a dry powder, containing the active drug pre-filled in a mixer container (Liproca Powder). The two components are, prior to injection, mixed under aseptic conditions to a paste, which will be transferred to a syringe, and administered with injection into the prostate.

For Part II, a target dose of 1800-2400 mg 2-HOF corresponding to approximately 30% of the prostate volume was planned as single dose. When deciding the total and individual dose to be injected, the total prostate volume, number of foci and total tumour volume were taken into consideration in each patient. If tumours were found in both lobes, the distribution of paste should be related to the amount of tumour in each lobe.

Administration was done by local injection of ready-mixed paste via rectum and with ultrasound guidance, in and around major tumour foci.

Number of subjects in period 2	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)	Treatment 8 weeks (Part II- 30vol% Liproca/ml prostate)
Started	18	5
Completed	18	5

Baseline characteristics

Reporting groups

Reporting group title	Baseline (Part I- 15vol% Liproca per ml prostate)
Reporting group description: Part I of the study, were the planned dose was 600-2000 mg 2-HOF and 6 weeks follow-up until prostatectomy.	
Reporting group title	Baseline (Part II - 30vol% Liproca per ml prostate))
Reporting group description: Part II of the study, where the planned dose was 1800-2400 mg 2-HOF and 8 weeks follow-up until prostatectomy.	

Reporting group values	Baseline (Part I- 15vol% Liproca per ml prostate)	Baseline (Part II - 30vol% Liproca per ml prostate))	Total
Number of subjects	18	5	23
Age categorical			
Patients between 50 and 75 years, both included, was the subject population.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	3	10
From 65-84 years	11	2	13
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	18	5	23
Protocol Deviations			
2 subjects were screened and included although they were not eligible according to the study protocol. Both patients were included in Part II of the study. - One patient was only 46 years old (incl. criteria from 50 years) - One patient had IPSS score > 17 at screening visit, but was re-assessed at Visit 2 with a IPSS score = 17 (excl. criteria if score is more than 17).			
Units: Subjects			
Protocol Deviation	0	2	2
Non-Protocol Deviation	18	3	21

End points

End points reporting groups

Reporting group title	Baseline (Part I- 15vol% Liproca per ml prostate)
Reporting group description: Part I of the study, where the planned dose was 600-2000 mg 2-HOF and 6 weeks follow-up until prostatectomy.	
Reporting group title	Baseline (Part II - 30vol% Liproca per ml prostate))
Reporting group description: Part II of the study, where the planned dose was 1800-2400 mg 2-HOF and 8 weeks follow-up until prostatectomy.	
Reporting group title	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)
Reporting group description: Part I of the study, where the planned dose was 600-2000 mg 2-HOF and 6 weeks follow-up until prostatectomy.	
Reporting group title	Treatment 8 weeks (Part II- 30vol% Liproca/ml prostate)
Reporting group description: Part II of the study, where the planned dose was 1800-2400 mg 2-HOF and 8 weeks follow-up until prostatectomy.	

Primary: Histopathological changes - Visible nucleoli

End point title	Histopathological changes - Visible nucleoli ^[1]
End point description: Visible nucleoli was unchanged in non-affected tumour tissue at last visit compared to Baseline (Day 1).	
End point type	Primary
End point timeframe: End of Study Visit compared to baseline (Day 1).	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done for the study. Only descriptive results available.

End point values	Baseline (Part I- 15vol% Liproca per ml prostate)	Baseline (Part II - 30vol% Liproca per ml prostate))	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)	Treatment 8 weeks (Part II- 30vol% Liproca/ml prostate)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	5	18	5
Units: Visible nucleoli	17	5	18	5

Statistical analyses

No statistical analyses for this end point

Primary: Histopathological changes - Nucleus hyperchromasia

End point title	Histopathological changes - Nucleus hyperchromasia ^[2]
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End point description:

Nucleus hyperchromasia (darker than normal staining pattern in the nucleus) was unchanged in non-affected tumour tissue at last visit compared to baseline (day 1).

End point type	Primary
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End point timeframe:

End of Study visit compared to baseline (Day 1).

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done for the study. Only descriptive results available.

End point values	Baseline (Part I- 15vol% Liproca per ml prostate)	Baseline (Part II - 30vol% Liproca per ml prostate))	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)	Treatment 8 weeks (Part II- 30vol% Liproca/ml prostate)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	5	18	5
Units: Nucleus hyperchromasia	18	5	18	5

Statistical analyses

No statistical analyses for this end point

Primary: Histopathological changes - Cytoplasm/nucleus ratio

End point title	Histopathological changes - Cytoplasm/nucleus ratio ^[3]
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End point description:

A decreased cytoplasm/nucleus (C:N) ratio (i.e. increased nucleus/cytoplasm ratio) is commonly associated with precancerous dysplasia as well as with malignant cells.

End point type	Primary
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End point timeframe:

End of Study Visit compared to Day 1 (baseline).

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done for the study. Only descriptive results available.

End point values	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)	Treatment 8 weeks (Part II- 30vol% Liproca/ml prostate)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	5		
Units: Increase of cytoplasm/nucleus ratio	10	1		

Statistical analyses

No statistical analyses for this end point

Primary: Histopathological changes - Cytoplasmic clearing

End point title Histopathological changes - Cytoplasmic clearing^[4]

End point description:

End point type Primary

End point timeframe:

End of Study visit compared to Day 1 (baseline)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done for the study. Only descriptive results available.

End point values	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)	Treatment 8 weeks (Part II- 30vol% Liproca/ml prostate)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	5		
Units: Increase of cytoplasmic clearing	10	0		

Statistical analyses

No statistical analyses for this end point

Primary: Histological visual results - Histopathologic alterations

End point title Histological visual results - Histopathologic alterations^[5]

End point description:

End point type Primary

End point timeframe:

End of Study Visit compared to Day 1 (baseline).

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done for the study. Only descriptive results available.

End point values	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)	Treatment 8 weeks (Part II- 30vol% Liproca/ml prostate)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	5		
Units: Histopathological alterations	12	2		

Statistical analyses

No statistical analyses for this end point

Primary: MRI visual results - MR changes global effect

End point title MRI visual results - MR changes global effect^[6]

End point description:

End point type Primary

End point timeframe:

End of Study Visit compared to (baseline).

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done for the study. Only descriptive results available.

End point values	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)	Treatment 8 weeks (Part II- 30vol% Liproca/ml prostate)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: MR changes global effect	6	3		

Statistical analyses

No statistical analyses for this end point

Primary: MRI visual results - MR changes tumour effect

End point title MRI visual results - MR changes tumour effect^[7]

End point description:

End point type Primary

End point timeframe:

End of Study Visit compared to baseline.

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done for the study. Only descriptive results available.

End point values	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)	Treatment 8 weeks (Part II- 30vol% Liproca/ml prostate)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	4		
Units: MR changes tumour effect	11	1		

Statistical analyses

No statistical analyses for this end point

Primary: Apparent diffusion coefficient (ADC) in index lesion by MRI

End point title	Apparent diffusion coefficient (ADC) in index lesion by MRI ^[8]
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End point description:

Apparent diffusion coefficient (ADC) measures the magnitude of water diffusion within tissue. An increased value for ADC indicates an anti-androgen effect, as a decreased cell density in tumour tissue results in an increased magnitude of water diffusion.

Images for measuring ADC was collected at baseline (Day 1) and End of Study (after 6 or 8 weeks), both in index lesion (site of main tumour in prostate) and in non-index lesion (other sites of tumour tissue in prostate).

End point type	Primary
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End point timeframe:

End of Study Visit compared to Day 1 (baseline).

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done for the study. Only descriptive results available.

End point values	Baseline (Part I- 15vol% Liproca per ml prostate)	Baseline (Part II - 30vol% Liproca per ml prostate))	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)	Treatment 8 weeks (Part II- 30vol% Liproca/ml prostate)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	5	12	3
Units: ADC in index lesion				
median (full range (min-max))	1125 (820 to 1598)	951 (592 to 1166)	1279 (831 to 1737)	689 (669 to 979)

Statistical analyses

No statistical analyses for this end point

Primary: Apparent diffusion coefficient (ADC) in non-index lesion by MRI

End point title	Apparent diffusion coefficient (ADC) in non-index lesion by
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End point description:

End point type	Primary
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End point timeframe:

End of Study Visit compared to Day 1 (baseline).

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done for the study. Only descriptive results available.

End point values	Baseline (Part I- 15vol% Liproca per ml prostate)	Baseline (Part II - 30vol% Liproca per ml prostate))	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)	Treatment 8 weeks (Part II- 30vol% Liproca/ml prostate)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	3	5	1
Units: ADC in non-index lesion				
median (full range (min-max))	1180.5 (1028 to 1723)	992 (0 to 1247)	1212 (976 to 1948)	955 (955 to 955)

Statistical analyses

No statistical analyses for this end point

Primary: Size of index lesion by MRI

End point title	Size of index lesion by MRI ^{[10][11]}
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End point description:

Only descriptive data available from Part I of the study.

The median size of index lesion in the prostate for 13 measurable patient was 1.40 cm (length), 0.90 cm (width) and 1.20 m (height).

There were only 4 patients who had measurements also at week 6, none showed a significant change of the tumour size.

End point type	Primary
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End point timeframe:

End of Study Visit (6 weeks) compared to Day 1 (baseline).

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was done for the study. Only descriptive results available.

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data has only been reported for patients in Part II. No summary results available.

End point values	Baseline (Part I- 15vol% Liproca per ml prostate)	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	4		
Units: Size of index lesion				
number (not applicable)	0	0		

Attachments (see zip file)	MRI index tumour/Figure 1a. MRI index tumour.png MRI index tumour - post treatment/Figure 1b. MRI index
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Statistical analyses

No statistical analyses for this end point

Primary: Histological visual results - Stroma reduction/cell clustering

End point title	Histological visual results - Stroma reduction/cell clustering ^[12]
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End point description:

End point type	Primary
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End point timeframe:

End of Study Visit compared to Day 1 (baseline).

Only done for Part II: The patients were followed for 8 weeks after injection and until prostatectomy was done.

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint was added to Part II after completion of Part I, hence no data available for patients in Part I.

End point values	Treatment 8 weeks (Part II- 30vol% Liproca/ml prostate)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Stroma reduction/ cell clustering	1			

Statistical analyses

No statistical analyses for this end point

Secondary: (Cho+PA+Cr)/Cit spectral intensity ratio - 2D MRSI

End point title	(Cho+PA+Cr)/Cit spectral intensity ratio - 2D MRSI
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End point description:

Intraprostatic tumour growth is associated with increased cell membrane turnover and increased cell proliferation, which lead to altered relative concentrations of certain metabolites included creatine (Cr), choline (Cho), polyamines (PA) and citrate (Cit), most specifically an increase in choline and a decrease in citrate. The effect of Liproca Depot was assessed by quantification of (Cho+PA+Cr)/Cit before treatment (baseline) and after treatment (week 6, or week 8).

End point type	Secondary
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End point timeframe:

End of Study Visit compared to Day 1 (baseline).

End point values	Baseline (Part I- 15vol% Liproca per ml prostate)	Baseline (Part II - 30vol% Liproca per ml prostate))	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)	Treatment 8 weeks (Part II- 30vol% Liproca/ml prostate)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10 ^[13]	4	6	4
Units: (Cho+PA+Cr)/Cit spectral intensity ratio				
median (full range (min-max))	0.62 (0.28 to 2.13)	1.099 (0.817 to 2.911)	1.91 (0.55 to 25.2)	1.569 (0.81 to 2.154)

Notes:

[13] - Only site Uppsala

Statistical analyses

No statistical analyses for this end point

Secondary: (Cho+PA+Cr)/Cit spectral intensity ratio - Single-voxel MRS

End point title	(Cho+PA+Cr)/Cit spectral intensity ratio - Single-voxel MRS ^[14]
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End point description:

End point type	Secondary
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End point timeframe:

End of Study Visit (6 weeks) compared to Day 1 (baseline).

Only done for Part I.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data has only been reported as comments to each patient in Part II. No summary results available.

End point values	Baseline (Part I- 15vol% Liproca per ml prostate)	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7 ^[15]	7		
Units: (Cho+PA+Cr)/Cit spectral intensity ratio				
median (full range (min-max))	0.75 (0.41 to 0.86)	1.22 (0.69 to 1.56)		

Notes:

[15] - Only site Uppsala

Statistical analyses

No statistical analyses for this end point

Secondary: (Cho+PA+Cr)/H2O spectral intensity ratio

End point title	(Cho+PA+Cr)/H2O spectral intensity ratio ^[16]
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End point description:

The variables (Cho+PA+Cr)/H2O spectral intensity ratio and Cit/H2O spectral intensity ratio before and after treatment were added as a complement to the variable (Cho+PA+Cr)/Cit . The difference in (Cho+PA+Cr)/Cit may be difficult to evaluate if the Cit and PA concentrations decrease close to the noise level, the Cho concentration increases and the Cr concentration change is small. The H2O concentration is not expected to change before and after treatment, why changes in these ratios may be reliable.

End point type	Secondary
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End point timeframe:

End of Study Visit (week 6) compared to Day 1 (baseline).

Done only for Part I.

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data has only been reported as comments to each patient in Part II. No summary results available.

End point values	Baseline (Part I- 15vol% Liproca per ml prostate)	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[17]	6		
Units: (Cho+PA+Cr)/H2O				
median (full range (min-max))	0.0019 (0.0016 to 0.0037)	0.0016 (0.0015 to 0.0023)		

Notes:

[17] - Only site Uppsala

Statistical analyses

No statistical analyses for this end point

Secondary: Cit/H2O spectral intensity ratio

End point title	Cit/H2O spectral intensity ratio ^[18]
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End point description:

The variables (Cho+PA+Cr)/H2O spectral intensity ratio and Cit/H2O spectral intensity ratio before and after treatment were added as a complement to the variable (Cho+PA+Cr)/Cit . The difference in (Cho+PA+Cr)/Cit may be difficult to evaluate if the Cit and PA concentrations decrease close to the noise level, the Cho concentration increases and the Cr concentration change is small. The H2O concentration is not expected to change before and after treatment, why changes in these ratios may be reliable.

End point type	Secondary
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End point timeframe:

End of Study Visit (week 6) compared to Day 1 (baseline).

Done only for Part I.

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data has only been reported as comments to each patient in Part II. No summary results available.

End point values	Baseline (Part I- 15vol% Liproca per ml prostate)	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[19]	6		
Units: Cit/H2O spectral intensity ratio				
median (full range (min-max))	0.0035 (0.0029 to 0.0066)	0.0019 (0.0012 to 0.0033)		

Notes:

[19] - Only site Uppsala

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma PSA

End point title	Plasma PSA
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End point description:

End point type	Secondary
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End point timeframe:

For Part I: Baseline (Day 1) and End of Study Visit (week 6)

For Part II: Baseline (Day 1) and End of Study Visit (week 8)

End point values	Baseline (Part I- 15vol% Liproca per ml prostate)	Baseline (Part II - 30vol% Liproca per ml prostate))	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)	Treatment 8 weeks (Part II- 30vol% Liproca/ml prostate)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	5	18 ^[20]	4 ^[21]
Units: ng/ml				
median (full range (min-max))	6.9 (2.2 to 18)	11 (3.8 to 14.6)	5.5 (1.7 to 10.5)	5.3 (3.1 to 12.4)

Notes:

[20] - End of Study

[21] - End of Study

Attachments (see zip file)	Figure 3. PSA % change from baseline.PNG
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Statistical analyses

No statistical analyses for this end point

Secondary: Changes in prostate volume

End point title	Changes in prostate volume
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End point description:

End point type	Secondary
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End point timeframe:

Baseline (Day 1) compared to 4 weeks (only Part I) and End of Study (6 weeks or 8 weeks).

End point values	Baseline (Part I- 15vol% Liproca per ml prostate)	Baseline (Part II - 30vol% Liproca per ml prostate))	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)	Treatment 8 weeks (Part II- 30vol% Liproca/ml prostate)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	5	18	5
Units: Prostate volume in ml				
median (full range (min-max))	31.15 (21 to 65)	28.4 (19 to 76)	28.8 (17 to 61.6)	27.5 (25 to 56.6)

Attachments (see zip file)	Figure 4. Prostate volume - change in % from baseline.PNG
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Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters harmonized - Tmax

End point title	Pharmacokinetic parameters harmonized - Tmax
End point description:	Safety variable. Data reported calculated based on the original scheduled time points.
End point type	Other pre-specified
End point timeframe:	Only for Part I: Pharmacokinetic samples were summarized for samples taken at baseline (Day 1), after 7 days, 28 days and at end of study (week 6).

End point values	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: day				
median (full range (min-max))	7 (7 to 7)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters harmonized - Cmax

End point title	Pharmacokinetic parameters harmonized - Cmax
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End point description:

Safety variable. Data reported calculated based on the original scheduled time points.

End point type	Other pre-specified
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End point timeframe:

Only for Part I: Pharmacokinetic samples were summarized for samples taken at baseline (Day 1), after 7 days, 28 days and at end of study (week 6).

End point values	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: ng/mL				
median (full range (min-max))	76.9 (20 to 182)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters harmonized - T last

End point title	Pharmacokinetic parameters harmonized - T last
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End point description:

Safety variable. Data reported calculated based on the original scheduled time points.

End point type	Other pre-specified
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End point timeframe:

Only for Part I: Pharmacokinetic samples were summarized for samples taken at baseline (Day 1), after 7 days, 28 days and at end of study (week 6).

End point values	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: day				
median (full range (min-max))	42 (7 to 42)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters harmonized - AUC all

End point title	Pharmacokinetic parameters harmonized - AUC all
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End point description:

Safety variable. Data reported calculated based on the original scheduled time points.

End point type	Other pre-specified
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End point timeframe:

Only for Part I: Pharmacokinetic samples were summarized for samples taken at baseline (Day 1), after 7 days, 28 days and at end of study (week 6).

End point values	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: day*ng/mL				
median (full range (min-max))	1272.4 (423 to 2838)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters harmonized - AUC 7d

End point title	Pharmacokinetic parameters harmonized - AUC 7d
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End point description:

Safety variable. Data reported calculated based on the original scheduled time points.

End point type	Other pre-specified
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End point timeframe:

Only for Part I: Pharmacokinetic samples were summarized for samples taken at baseline (Day 1), after 7 days, 28 days and at end of study (week 6).

End point values	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: day*ng/mL				
median (full range (min-max))	269.2 (68 to 636)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters harmonized - AUC 28d

End point title	Pharmacokinetic parameters harmonized - AUC 28d
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End point description:

Safety variable. Data reported calculated based on the original scheduled time points.

End point type	Other pre-specified
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End point timeframe:

Only for Part I: Pharmacokinetic samples were summarized for samples taken at baseline (Day 1), after 7 days, 28 days and at end of study (week 6).

End point values	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: day*ng/mL				
median (full range (min-max))	1171.5 (392 to 2838)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters harmonized - AUC 42d

End point title	Pharmacokinetic parameters harmonized - AUC 42d
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End point description:

Safety variable. Data reported calculated based on the original scheduled time points.

End point type	Other pre-specified
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End point timeframe:

Only for Part I: Pharmacokinetic samples were summarized for samples taken at baseline (Day 1), after 7 days, 28 days and at end of study (week 6).

End point values	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: day*ng/mL				
median (full range (min-max))	1339.1 (558 to 2667)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters observed - Tmax

End point title	Pharmacokinetic parameters observed - Tmax
End point description: Safety variable. Data reported calculated based on the original scheduled time points.	
End point type	Other pre-specified
End point timeframe: Only for Part I: Pharmacokinetic samples were summarized for samples taken at baseline (Day 1), after 7 days, 28 days and at end of study (week 6).	

End point values	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: day				
median (full range (min-max))	7 (5 to 11)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters observed - Cmax

End point title	Pharmacokinetic parameters observed - Cmax
End point description: Safety variable. Data reported calculated on the actual time points when plasma samples were taken.	
End point type	Other pre-specified
End point timeframe: Only for Part I: Pharmacokinetic samples were summarized for samples taken at baseline (Day 1), after 7 days, 28 days and at end of study (week 6).	

End point values	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: ng/mL				
median (full range (min-max))	76.9 (19 to 182)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters observed - T last

End point title	Pharmacokinetic parameters observed - T last
End point description:	
Safety variable.	Data reported calculated on the actual time points when plasma samples were taken.
End point type	Other pre-specified
End point timeframe:	
Only for Part I:	Pharmacokinetic samples were summarized for samples taken at baseline (Day 1), after 7 days, 28 days and at end of study (week 6).

End point values	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: day				
median (full range (min-max))	40 (7 to 49)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Pharmacokinetic parameters observed - AUC all

End point title	Pharmacokinetic parameters observed - AUC all
End point description:	
Safety variable.	Data reported calculated on the actual time points when plasma samples were taken.
End point type	Other pre-specified

End point timeframe:

Only for Part I: Pharmacokinetic samples were summarized for samples taken at baseline (Day 1), after 7 days, 28 days and at end of study (week 6).

End point values	Treatment 6 weeks (Part I - 15vol% Liproca/ml prostate)			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: day*ng/mL				
median (full range (min-max))	1219.4 (423 to 2949)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first patient visit in Part I: 09 MAY 2012 until last patient visit Part II: 18 MAY 2015.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.0
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Reporting groups

Reporting group title	Part I: 18 patients
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Reporting group description:

Part I of the study, where the planned dose was 600-2000 mg 2-HOF and 6 weeks follow-up until prostatectomy.

Reporting group title	Part II: 5 patients
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Reporting group description:

Part II of the study, where the planned dose was 1600-2400 mg 2-HOF and 8 weeks follow-up until prostatectomy.

Serious adverse events	Part I: 18 patients	Part II: 5 patients	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	2 / 5 (40.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Sepsis			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 18 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pelvic pain	Additional description: Pelvic pain caused by urinary retention		
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 18 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part I: 18 patients	Part II: 5 patients	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 18 (55.56%)	4 / 5 (80.00%)	
Investigations			
C-reactive protein increased			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 18 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Sepsis	Additional description: State after sepsis		
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 18 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Prostatic pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Oedema genital	Additional description: Oedema of the right prostate lob		
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 18 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Haematospermia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	2 / 18 (11.11%)	1 / 5 (20.00%)	
occurrences (all)	2	1	
Dysuria			
subjects affected / exposed	4 / 18 (22.22%)	3 / 5 (60.00%)	
occurrences (all)	5	3	
Urinary retention			
subjects affected / exposed	1 / 18 (5.56%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Bladder irritation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Stress urinary incontinence			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 18 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Pollakiuria			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 18 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Prostatic abscess			
subjects affected / exposed	1 / 18 (5.56%)	0 / 5 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2011	Amendment 1: The substantial change in the amendment was that if a biopsy at diagnosis was not performed as described in the protocol, another biopsy using the biopsy mapping described should be taken approximately 6 weeks before the first MRI. There were also some non-substantial changes, e.g. time between first MRI and day of injection, removal of questionnaire, emphasis on noting the correct dosing when injecting both lobes and volume blood in sample for PK.
12 May 2014	Amendment 2: The extension of the study with another 10 patients at a higher dosage of Liproca (up to 2 400 mg), and a time period of 6 - 8 weeks between the Liproca administration and the prostatectomy was described in the second amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported