Final Clinical Study Report Synopsis

LPC-002

An open, single and multiple dose, efficacy and safety Proof of Principle study of Liproca® Depot, a controlled release formulation of 2-hydroxyflutamide, injected into the prostate in patients with localized prostate cancer

Product	Liproca® Depot
Development Phase of Trial	Phase IIa (Proof of Principal)
Indication	Localized prostate cancer (T_1-T_2)
Trial Initiation Date	2009-05-11 (FIMEA approval)
Trial Completion Date (Part I)	2011-05-11 (Last patient, last visit)
Trial Completion Date (Part II)	2011-06-20 (Last patient, last visit)
Co-ordinating Investigator	Professor Teuvo Tammela, Dept. of Surgery, Tampere University Hospital, Tampere, Finland.
Sponsor	LIDDS AB Kullagatan 8 252 20 Helsingborg, Sweden

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LIDDS AB

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2 SYNOPSIS

Name of Company: LIDDS AB **Name of Finished Product:** Liproca® Depot **Name of Active Ingredient:** 2-hydroxyflutamide (2-HOF)	**Individual study table referring to part of the dossier** **Volume:** **Page:**	(For national authority use only)

Title of study:

An open, single and multiple dose, efficacy and safety Proof of Principle study of Liproca® Depot, a controlled release formulation of 2-hydroxyflutamide, injected into the prostate in patients with localized prostate cancer.

Study number: LPC-002

EudraCT number:
2009-010079-25

Co-ordinating Investigator(s): Professor Teuvo Tammela. Dept. of Surgery, Tampere University. Hospital, Tampere, Finland.

Study center(s):

Dept. of Surgery, Division of Urology, Tampere Univ. Hospital, Tampere, Finland.

Dept. of Surgery, Division of Urology, Helsinki Univ. Hospital, Helsinki, Finland.

Dept. of Surgery, Division of Urology, Päijät-Häme Central Hospital, Lahti, Finland.

Publication (reference):

Studied period (years): Max.24 weeks (Part I)
+ max. 24 weeks (Part II).

Phase of development: II a

Primary Objective:

Part I
To evaluate efficacy of a single injection of Liproca® Depot in patients with localized prostate cancer.

Part II
To evaluate efficacy after a second injection.

Secondary Objectives:

To evaluate safety and Quality of Life of a single and a second injection of Liproca® Depot in patients with localized prostate cancer and to follow the pharmacokinetic and pharmacodynamics profile of Liproca® Depot.

Study Design: An open, non-randomized, single and multiple dose, efficacy and safety multicentre study, with the aim to show "Proof of Principle". Patients with localized prostate cancer were followed to progression or maximum 24 weeks after a single injection in one lobe of 2 -8 mL ready-made paste (corresponding to 400 – 1600 mg 2-HOF) of Liproca® Depot. Patients who progressed (defined as an increase in PSA by ≥ 25 % over baseline or on-treatment nadir, confirmed by a second measurement 2 weeks later) within 24 weeks were offered a second injection with Liproca® Depot (2 -8 mL ready-made paste, corresponding to 400 - 1600 mg 2-HOF), and followed to progression or maximum 24 weeks after the second injection. If the patient did not agree to a second injection in the same lobe he left the study, and was treated at the Investigator's discretion. Efficacy was measured primarily as PSA nadir, and secondly as time to PSA nadir and prostate volume change. Safety and quality of life were monitored throughout the whole study period.

Number of patients (planned and analysed):

Planned: With an expected proportion of 0.15 of the patients being not evaluable for efficacy, 24 patients were planned to be included in the trial.

Analysed:

Twenty-four (24) patients were included in Part I, and 9 patients were included in Part II of the study. All patients were included in the analysis of both efficacy and safety**.**

Diagnosis and main criteria for inclusion:
Diagnosis: Localized prostate cancer (T_1-T_2)

Inclusion criteria:

1) Age ≥ 45years
2) Histologically confirmed localized prostate cancer (T_1-T_2), predominantly in one side of the peripheral zone, verified by biopsy.
3) PSA value < 20 ng/mL within 6 weeks before enrolment.
4) Gleason score ≤ 3+4 at diagnostic biopsy
5) Adequate renal function: Creatinine ≤ 1.5 times upper limit of normal.
6) Adequate hepatic function: ASAT, ALAT and ALP ≤ 1.5 times upper limit of normal.
7) Negative dipstick for bacturia.
8) Patient must have ability to cope with the study procedures and to return to scheduled visits including follow up visit.

Exclusion criteria:

1) Previous or ongoing hormone therapy for prostate cancer.
2) Ongoing or previous therapy (within 3 month) of finasteride or dutasteride.
3) Ongoing or previous invasive therapy for benign prostate hyperplasia (TURP, TUMT).
4) Symptoms or signs of acute prostatitis.
5) Symptoms or signs of ulceric proctitis
6) Severe micturation symptoms (I-PSS >17)

7) Concomitant systemic treatment with corticosteroids, or immunomodulating agents.
8) Known immunosuppressive disease (*e.g.* HIV, insulin dependent diabetes).
9) Simultaneous participation in any other study involving not market authorized drugs or having participated in a study within the last 12 months prior to start of study treatment.

Test product, dose and mode of administration, batch number:

Test Product: Liproca® Depot. A parenteral controlled release depot formulation of 2-hydroxyflutamide (2-HOF).

Batch number: Liproca® Depot 2447379
(Liproca Powder 2391386, Liproca Diluent CMC 2378208)

Dose: The amount of Liproca® Depot injected was 2 - 8 mL ready-made paste which corresponds to 400 – 1600 mg 2-HOF. Thirteen patients were injected in the right prostate lobe and 11 patients were injected in the left prostate lobe. The mean amount of Liproca® Depot injected in Part I was 3.58 mL (range 2.0 - 7.8 mL). The mean amount of Liproca® Depot injected in Part II was 3.32 mL (range 3.0 - 4.0 mL).

Ex tempore preparation and administration: The product consists of two sterile components, one aqueous liquid and a dry powder, containing the active drug 2-HOF. The two components were mixed under aseptic conditions to a paste prior to administration, which was administered by trans rectal ultrasound (TRUS) guided injection into the prostate gland within the lobe area where the tumour tissue had been localized.

Duration of treatment:
TRUS guided injection of a single dose of Liproca® Depot and close monitoring of efficacy and safety during maximum 24 weeks.

TRUS guided injection of a second dose (in the same lobe) in patients progressing after 1st injection, with close monitoring of efficacy during maximum 24 weeks.

Criteria for evaluation:

Efficacy:

Primary efficacy variable:

- Proportion of patients showing PSA nadir (based on concentration of PSA in plasma)

Secondary efficacy variables:

- Prostate volume change with ultrasound screening.
- Time to PSA nadir.

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Safety:

Secondary safety variables:

- Adverse events caused by the study treatment
- Abnormal, clinically relevant, laboratory parameters
- Voiding symptoms (I-PSS)

- Vital signs
- Quality of Life

Pharmacokinetic variables:

- AUC, C_{max}, T_{max}, $T_{1/2}$ of 2-hydroxyflutamide
- 2-hydroxyflutamide concentration and its metabolites in urine

Statistical methods:
The primary efficacy variable was the confirmed treatment success rate, defined as plasma PSA value being lower compared to any value preceding the measurement (*i.e.* plasma PSA nadir).

The inter patient variation of plasma PSA between screening (S) and baseline (B) showed that the accuracy of estimates of the start value for each patient improved when using the mean value of the screening and baseline values (SB). This is considered as the most accurate value and was accordingly applied as the primary comparison (Part I). Baseline (B) and screening (S) values have also been used as starting values and sensitivity of these analyses are discussed in this report.

Two subgroups have been added to the analysis of Part I. Responders (*i.e.* patients who have reached plasma PSA nadir) and completers (*i.e.* patients who have been attending all visits *i.e.* 24 weeks). These two subgroups have been added to all analyses regarding plasma PSA, prostate volume and testosterone (Part I).

Responders have also been analysed as patients who have plasma PSA values below the start value at least 2, 3, 4, 5 or 6 consecutive times respectively, corresponding to 8, 12, 16, 20 or 24 weeks duration of effect on PSA.

Prostate volume nadir, defined as the lowest prostate volume value after baseline have been analysed using descriptive statistics.

Correlation between plasma PSA and prostate volume has been calculated by visit using Pearson correlation coefficient.

Plasma PSA (biochemical) progression was defined as an increase in PSA by ≥ 25 % over baseline or on-treatment nadir, confirmed by a second measurement 2 weeks later.

Success rate was estimated and 95 % confidence intervals were calculated. Time to plasma PSA nadir and time to prostate volume were calculated by the Kaplan-Meier method.

For variables of continuous type, numbers of observations (N), mean and/or median, standard deviation (SD), minimum and maximum are presented. Categorical variables are presented using frequencies and percentages.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Part I:

All 24 patients were Caucasian men, with a mean age at inclusion of 68.4 years (range 55-80 years). Among the 24 patients enrolled in Part I the primary endpoint plasma PSA

nadir was reached by 20 patients (responders). Based on this the study had 83 % success rate with a 95 % confidence interval (CI) [95 % CI: 63-95]. The primary endpoint was analysed by using the mean of screening (S) and baseline (B) values as the starting value. The success rate when using baseline or screening as starting point was 75 % [95 % CI: 53-90] and 87.5 % [95 % CI: 68-97], respectively. These three different analyses of the primary endpoint showed very similar results.

The mean reduction of plasma PSA nadir from the mean of screening and baseline was 24.9 % (SD 13.79). In this group of responders the median time to PSA nadir was 56 days with a [95 % CI: 28-118]. The mean plasma PSA concentration-time profile among the 20 responders was significantly reduced at week 4, 12, 16 and 20. This demonstrates that the effect duration on PSA of a single dose of Liproca® Depot injected in only one lobe lasts at least 16-20 weeks.

The median time to plasma PSA nadir was 77 days [95 % CI: 32-126] for all patients. This delay of time to plasma PSA nadir for all 24 patients compared to the 20 responders was due to the 4 patients that did not reach plasma PSA nadir for different reasons. Accordingly, the mean plasma PSA concentration-time was unaffected for these 24 patients. In the subgroup completers (15 patients that stayed in the study for the entire study period, 24 weeks) the median time to PSA nadir was 91 days [95 % CI: 34 -140].

A significant decrease in prostate volume was seen in at each visit compared to baseline for all patients. The per cent reduction from baseline to nadir and final visit was 14 % (SD 9.6) ($p \leq 0.0001$) and 7 % ($p = 0.0041$), respectively. The median time to prostate volume nadir was 112 days with a [95 % CI: 21-184].

The mean per cent increase of serum testosterone from baseline to visit 5 (week 4) was 13.6 % ($p= 0.0032$), but the increase was not considered to be of clinical relevance. In the two subgroups (responders and completers) the serum testosterone was significantly increased at visit 5 (week 4) and at visit 10 (week 24) in the completer group, but also here considered to be of no clinical relevance.

The plasma concentrations of 2-HOF remained low throughout the dosing interval. There was a higher plasma exposure during the first week compared to latter time points, which is explained by the release of the drug from both the un-intended and intended boost doses of 2-HOF in Liproca® Depot. The C_{max} and C_{last} for 2-HOF in plasma were 83.02 (SD 45.97) and 2.67 (SD 2.66), respectively.

Voiding symptoms were judged at each visit, and none of the changes were statistically significant. Most of the patients had mild or moderate IPSS when included in the study.

<u>Part II:</u>

<u>Nine patients was injected a second dose of Liproca® Depot.</u>

The primary endpoint, plasma PSA nadir, showed a 67 % success rate [95 % CI: 30-93].

The mean plasma PSA concentration-time profile was unaffected for either the absolute change or the per cent change over time. The median time to PSA nadir was 154 days [95 % CI: 53-].
The per cent change and the absolute change of serum testosterone from baseline to visit 5 (week 4) showed a statistically significant difference (p= 0.0156), but considered to be of no clinical relevance.

Prostate volume significantly decreased over time from baseline to visit 7 (week 12), both in absolute change and in per cent change. The per cent change from baseline to visit 7 was 5 % (p= 0.0469).

The C_{max} and C_{last} for 2-HOF in plasma were 72.07 (SD 30.96) and 7.20 (SD 14.98), respectively.

SAFETY RESULTS:

The safety profile for study part I and II were similar and the general conclusion for both parts of the study was:
The voiding scale was measured at each visit, and none of the changes was statistically significant. All the patients had mild or moderate IPSS when included in the study.
Quality of life, measured by EORTC PR25, was not affected by the treatment. The administration of Liproca® Depot did neither affect the sexual function nor the sexual activity.
The overall conclusion is that treatment with Liproca® Depot was well tolerated, with few adverse events of which only two were considered to be serious (One (1) in Part 1 and one (1) in Part II). In both cases it was a prostate infection which was considered to be related to the injection technique of the study drug. Both the serious cases were effectively treated with antibiotics.
No major changes could be seen in either the laboratory data or in the vital signs.

Part I: There were 22 patients reporting at least one adverse event. The most common adverse events reported were dysuria and haematuria, both of which were reported by six patients. One patient reported a serious adverse event, prostate infection, which was judged related to the injection technique.

The voiding scale was measured at each visit, and none of the changes was statistically significant. Most of the patients had mild or moderate IPSS.

Part II:

There were 7 patients reporting at least one adverse event. In total 22 adverse events were reported and 7 of these were judged by the investigator as possibly or probably related to the treatment. The most common adverse events reported were pollakiuria and haematuria, each reported by two patients. One patient reported a serious adverse event, prostate infection, which was judged related to the injection technique.

CONCLUSIONS:

The study was well conducted in all aspects with high data quality. The primary endpoint showed interesting results with high success rate (83 %), *i.e*. proportion of patients (responders) that reached plasma PSA nadir. Among the responders there was effect duration of at least 16-20 weeks. The reduction of plasma PSA and prostate volume was significant at week 4, 12, 16 and 20. This demonstrates that the effect duration on PSA of a single dose of Liproca® Depot may last at least 16-20 weeks. The effect on plasma PSA and prostate volume was compared with corresponding data from oral administration with flutamide. Even if the effects reported following oral administration of flutamide was higher, the effects obtained after dosing with Liproca® Depot are clinically promising as not the optimal dose was given and only one lobe per patient was treated. In the future, higher doses are expected to given with Liproca® Depot .
The minor effect on serum testosterone at an early and one late time point was not considered to be of any clinical relevance. The plasma concentration of 2-HOF remained low throughout the dosing interval.

In general very few adverse events were reported, which is expected from the low systemic exposure o 2-HOF. The most common were renal and urinary related disorders which were expected and are common events after biopsy. Two infections were reported and were effectively treated with antibiotics. They were considered to be due to the trans rectal ultrasound injection (same as with biopsy)

All together the results justify further clinical studies in order to investigate the clinical effect of Liproca® Depot.

Date of the report: 2012-05-14 (Final)