Study synopsis

Provide a structured synopsis containing all important information, preferably in tabular view:

Sponsor / Sponsor-Investigator	Dr. med. Jean-Luc Fehr
Study Title:	A Prospective Single Arm Observational Study Evaluating Focal Therapy using High Intensity Focused Ultrasound (Sonablate 500) for Localised Prostate Cancer
Short Title / Study ID:	Evaluating Focal Therapy using High Intensity Focused Ultrasound for Localised Prostate Cancer
Protocol Version and Date:	Version 01, 06.05.2015
Trial registration:	Internationales Primärregister: www.clinicaltrials.gov Nationales Register: SNCTP Register
Study category and Rationale	Category A: The HIFU Therapy is established and applied internationally as well as in Switzerland. No changes to standard therapy are performed in this study (CHOP Code 60.99.11). Medical doctor and medical team are trained accordingly at UCL. The trial is conducted to collect data on side effects and long-term outcomes of this particular therapy.
Clinical Phase:	Observational Study

Background and Rationale:	Men with localised prostate cancer currently face a difficult decision between radical therapies and active surveillance. The former provides a greater certainty of cancer control but with a significant risk of side effects (50% impotence, 5-10% incontinence, 5-20% bowel dysfunction); the latter entails living with the diagnosis of untreated cancer and the risk of progression. High Intensity Focal Ultrasound (HIFU) aims at destroying specifically the cancer tissue through high temperature. This locally limited treatment is the best strategy to minimize side effects as surrounding, healthy tissue is not affected by the treatment. Further, the procedure is very gentle using no operative procedures with the treatment performed through the rectum. Due to all these advantages HIFU treatment is performed internationally and in Switzerland (CHOP code 60.99.11) since several years. However, little is known on long-term data on therapy outcome and side-effects of the therapy. Especially data on disease control or conversion of patients to radical therapy is sparse but needed since it cannot be completely excluded that cancer might develop on a different location in the prostate. Still, focal therapy is a strategy that could complement the current choices available to men by offering potential functional preservation whilst ablating clinically significant cancer and monitoring untreated benign tissue or clinically insignificant cancer. The aim of this observational study is therefore to monitor the HIFU Therapy at Klinik Hirslanden Zurich and collect data on side effects and long-term outcomes after treatment.

Objective(s):	**Primary:** 1. To determine the proportion of men converting to radical therapy and/or requiring systemic therapy and/or developing metastases and/or dying of prostate cancer following focal therapy for localised prostate cancer using HIFU at 5 years after focal therapy using HIFU. 2. To determine the proportion of men converting to radical therapy and/or requiring systemic therapy and/or developing metastases and/or dying of prostate cancer following focal therapy for localised prostate cancer using HIFU at 10 years. Secondary: 1. To determine the following after focal therapy using HIFU: - rate of erectile dysfunction - time to return of erectile function - rate of loss of ejaculation - rate of loss of orgasm - rate of pain during intercourse - number of men using phosphodiesterase-5 inhibitors to maintain erectile function - rate of urinary incontinence (pad free, leak free and pad-free alone) - time to return of continence (pad free, leak free and pad-free alone) - rate of lower urinary tract symptoms - rate of bowel toxicity - anxiety levels - general health related quality of life - proportion of men achieving trifecta status at 12 and 24 months - risk factors for failure defined as a) presence of any cancer and b) clinically significant cancer at study end To analyse the following outcome parameters following focal therapy using HIFU: - biochemical (PSA) kinetics including determining the optimal biochemical definition of failure - describe composite outcomes of failure 2. To determine the costs of treatment and model potential cost effectiveness, by comparison to overall histological and functional outcomes at 5 years and 10 years compared to other cohort trials involving the treatment of localized prostate cancer.

Outcome(s):	The primary outcome of the study will be disease control at 5 and 10 years. Disease control will be measured rates of conversion to radical therapy and/or requirement for systemic therapy (hormones/chemotherapy) and/or development of metastases and/or prostate-related mortality following focal therapy for localised prostate cancer using HIFU at 5 and 10 years. Secondary outcomes will be assessed using validated patient questionnaires, including the evaluation of urinary, erectile, and bowel toxicity, and anxiety levels. In addition, we aim to determine the potential cost-effectiveness of this new therapeutic pathway.
Study design:	Prospective, mono-center, observational, single-arm cohort study, Category A, with 70 patients to be recruited at Klinik Hirslanden.

Inclusion / Exclusion criteria:	**Inclusion for HIFU Therapy (and therefore the observational study):** - Histologically proven prostate cancer on trans-rectal or transperineal template prostate biopsies - TRUS biopsy: up to burden bilateral disease with maximum 3mm one biopsy on non-dominant side is allowable. - MRI targeted and/or Template biopsy within 12 months of entry showing: unilateral disease any burden OR bilateral disease; presence of clinically significant cancer on only one side (as determined by histological rules described above) Gleason ≤7 - Stage T1-T2cN0M0 disease, as determined by local guidelines (radiological T3a permitted) - Serum PSA </=20 - Life expectancy of >/=10 years - Signed informed consent by patient and an understanding of the German language sufficient to understand written and verbal information about the trial and consent process **Exclusion for HIFU Therapy:** - Men who have had previous cancer treatment therapy - Men with evidence of metastatic disease or nodal disease outside the prostate on bone scan or cross-sectional imaging - Men with latex allergies or unable to tolerate a transrectal ultrasound - Men who have undergone prior significant rectal surgery preventing insertion of trans-rectal HIFU probe - Men who have had previous HIFU, cryosurgery, thermal or microwave therapy to the prostate. - Men who have undergone a Transurethral Resection of the Prostate (TURP) for symptomatic lower urinary tract symptoms within 6 months. - Men unable to have pelvic MRI scanning - Presence of metal implants/stents in the urethra - Presence of prostatic calcification and cysts (on transrectal ultrasound) whose location will interfere with effective delivery of HIFU therapy - Men with renal impairment with a GFR of <20ml/min (unable to tolerate Gadolinium dynamic contrast enhanced MRI).

Measurements and procedures:	**While the following information describes the whole HIFU-Therapy procedure, only the questionnaires (screening visit, 12 and 24 month) are solely for study purposes. CRF will be filled out for each visit.** Screening Visite Patient information about study procedures; Evaluation of in- and exclusion criteria; Evaluation of full medical history; Review of prostate biopsy results; Review of previous laboratory investigations; Determine PSA if not available within 6 month of entry; Review urinalysis If eligible: - signed informed consent form and patient questionnaire - multi-parametric MRI and targeted or template transperineal biopsy to localize tumor tissue HIFU Treatment (CHOP Code 60.99.11) HIFU treatment will be carried out as outlined in the protocol. Briefly, patient will be anaesthetized for HIFU treatment. HIFU ultrasound probe will be introduced transrectally and the carefully localized cancer tissue will be treated with heat to destroy cancer tissue. Patient will require a suprapubic catheter after procedure. Discharge is expected to be on the same day or the following day with a suprapubic catheter. 1-2 Weeks Post HIFU Ablation Catheter removal under antibiotic cover. Patients will be taught CISC (Clean Intermittent Self-Catheterization), if appropriate. 3 Months and 6 Months Post HIFU Ablation (This visit may be performed via a telephone consultation and arrangement for blood tests via the patient's family practitioner at the clinician's discretion): Adverse event reporting; Blood tests: PSA (locally with family practitioner is possible); Case report forms 12 Months Post HIFU Ablation Same procedure as 3 and 6 months with **questionnaire** at 12 months. If medically necessary a multi-parametric MRI and prostate biopsy of treated area will be performed. If the 12 month prostate biopsy identifies the presence of cancer in the treated area of ablation then the patient will be offered a second treatment (re-treatment) with focally delivered HIFU and the follow-up visits for the re-treatment HIFU will be the same as the primary HIFU treatment. 18 and 24 Months Post HIFU Ablation Same procedure as 3 and 6 months with a **questionnaire** only at the 24 months.

Study Product / Intervention:	No study specific medical interventions will be performed. The patient will undergo HIFU treatment according standard procedure. The patients will be asked to fill out questionnaires (12 und 24 months) to monitor the therapy and side effects. The study entails data gathering for the side-effects and long-term outcomes of HIFU therapy as too little data is available.
Control Intervention (if applicable):	N/A: Observational study
Number of Participants with Rationale:	Klinik Hirslanden: 70 patients
Study Duration:	12 years: - 2 years of recruitment with 24 month follow-up und follow-up after 5 und 10 years - Interimsanalyses: 4 years after recruitment of the last patient - Interims- und endanalyses: after 5 and 10 years Long-term data will be evaluated in collaboration with the University College of London (encrypted data (verschlüsselt))
Study Schedule:	01.01.2016 01.01.2028
Investigator(s):	Dr. med. Jean-Luc Fehr Klinik Hirslanden Witellikerstrasse 40 CH-8032 Zürich Telefon: 044 387 20 30 E-Mail: jean-luc.fehr@hirslanden.ch
Study Centre(s):	Monocentric in Switzerland Sponsor: Dr. med. Jean-Luc Fehr (Klinik Hirslanden) Collaboration with the University College of London, UK – Sponsor: Prof. Dr. med. Mark Emberton - University College London Hospital NHS, Foundation Trust - Basingstoke and North Hampshire NHS, Foundation Trust - Oxford Radcliffe Hospitals NHS Trust - Royal Marsden NHS Foundation Trust - University Hospitals Bristol NHS Foundation Trust - Betsi Cadwaladr University Health Board

Statistical Considerations:	Klinik Hirslanden - Interim analysis, 4 years after recruitment of the last patient: HIFU treatment aims at improving side effect of prostate cancer treatment compared to radical therapies. Thus, our goal is to monitor patient quality of life and treatment side effects 12 and 24 month after HIFU treatment using standard questionnaires with score system (EPIC, IIEF-15, IPSS). Mean scores for each time point will be calculated. Pre-treatment scores will be compared to scores obtained 12 months and 24 months after treatment using a two-sided t-test. Further, linear regression will be used to analyze the relationship between patient characteristics (e.g. PSA, Gleason score, and recurrence risk group) and specific questionnaire scores. In Collaboration- Endanalysis: In this trial the primary objective of stage two is to estimate the proportions of patients who convert to radical therapy and/or requiring systemic therapy and/or developing metastases and/or dying of prostate cancer following focal therapy for localised prostate cancer using HIFU at 5 and 10 years after focal therapy using HIFU. We assume that 10% at 5 years and 30% at 10 years will meet this endpoint (currently, 20-30% transition in this way after radical therapy at 8-10 years follow-up). Using a precision based calculation for 95% confidence intervals at least in which we expect a 95% confidence interval of 5% for the 30% proportion endpoint, a sample size of 318 is required. For the earlier endpoint of 10% at 5 years, and 5% 95% CI, a sample size of 138 is required. Therefore, aiming for the higher of the two sample sizes and a 10% non-compliance with long-term follow-up, a total sample size including stage one and stage two of N=350 is required. At Klinik Hirslanden the recruitment of 70 patients are planned. The end analysis (data on therapy conversion and disease outcome after 5 and 10 years) will, thus, be done in collaboration with the study centers in the United Kingdom to guarantee sufficient patient number. Interims analyses on patient quality of life and side effects will be done at Klinik Hirslanden 4 years after recruitment of last the patient.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

STUDY SUMMARY IN LOCAL LANGUAGE

Männern mit lokalem Prostatakrebs fehlt es an einer Alternativtherapie zwischen der radikalen Therapie (operativ oder bestrahlend) und dem Abwarten mit Überwachung. Während die erstere Therapie eine grössere Sicherheit bietet, dass die Krebserkrankung unter Kontrolle ist, bringt sie meist schwerwiegende Nebenwirkungen (Impotenz, Inkontinenz, Darmfunktionsstörungen) mit sich. Abwarten wiederum birgt Risiken, dass die Krebserkrankung fortschreitet und kann psychisch sehr belastend sein. Die hochfokussierte Ultraschalltherapie (HIFU) hat zum Ziel das genau lokalisierte Krebsgewebe mittels Hitze abzutöten, um so den Krebs mit minimalsten Nebenwirkungen zu bekämpfen, da möglichst wenig gesundes Gewebe beschädigt wird. Die HIFU-Therapie wird seit einigen Jahren international und in der Schweiz (im speziellen den Universitätsspitälern, CHOP code 60.99.11) angewendet und zeichnet sich durch positive Ergebnisse aus. Das gezielt lokalisierte Krebsgewebe wird bei der HIFU Therapie erfolgreich durch Hitze abgetötet, während die Nebenwirkungen durch beschädigtes, umliegendes Gewebe minimal gehalten werden können. Auch ist die Therapie schonend, da sie ohne operative Verfahren (die Sonde kann transrektal durch den Enddarm eingeführt werden) auskommt. Bis anhin fehlt es jedoch an genügend Daten über die Langzeitverläufe der so behandelten Patienten (Bsp. Rückfallrate, Benötigung einer radikalen Therapie und/oder Todesrate nach 5 bis 10 Jahren), da bei dieser Therapie nicht ausgeschlossen werden kann, dass sich der Krebs an einem anderen Ort in der Prostata weiterentwickelt, was meist eine radikale Therapie zur Folge hat. Das Ziel diese Beobachtungsstudie ist es die HIFU Therapie an der Klinik Hirslanden zu begleiten. Insbesondere wertvolle Daten über die Langzeitverläufe und die auftretenden Nebenwirkungen der Therapie sollen gewonnen werden.