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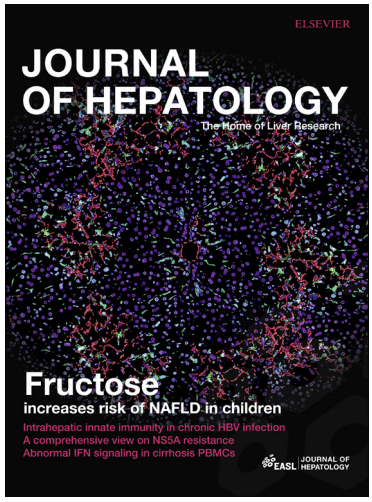

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alfapump System vs. Large Volume Paracentesis for Refractory Ascites: A Multicenter Randomized Controlled Study

Short title: alfapump treatment of refractory ascites

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Abbreviations:

AE: Adverse event

AKI: acute kidney injury

AP: alfapump

BMI: body mass index

CLDQ: chronic liver disease questionnaire

CONSORT: Consolidated Standards of Reporting Trials

EASL: European Association for the Study of Liver Disease

eMIT: electronic market information tool

HE: hepatic encephalopathy

HIV: human immunodeficiency virus

HRQoL: health related quality of life

ICER: incremental cost-effectiveness ratio

IQR: interquartile ratios

ITT: intention to treat

KIM-1: kidney injury molecule 1

LVP: large volume paracentesis

MELD: model for end-stage liver disease

MAMC: mid-arm muscle circumference

NGAL: neutrophil gelatinase-associated lipocalin

NHS: National Health-Care System

PICD: paracentesis-induced circulatory dysfunction

RA: refractory ascites

RFH-GA: Royal Free Hospital general assessment

SAE: serious adverse event

SoC: standard of care

TIPS: transjugular intrahepatic portosystemic shunt

TSF: triceps skin fold thickness

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Disclosures:

Rajiv Jalan has research collaborations with Ocera and Takeda. He is the Chief Investigator for a Sequana-sponsored study. Rajiv Jalan is the inventor of University College London-Liver Dialysis Device, Yaq-001 and a toll-like 4 antagonist, which has been patented by UCL and licensed to Yaqrit Limited, which a UCL spin out company. He also invented ornithine phenylacetate, which has been licensed by UCL to Ocera. Laure Elkrief had received funding from Sequana for reporting of the data into the CRF for this study. Dominique Valla received an honorarium from Sequana Medical for this clinical study, is a consultant on the Liver Safety Committee of Laboratoires Servier, and has provided teaching services for Gilead. Paolo Angeli is a member of the Sequana Medical AG Advisory Board, the LAT Pharma LLC

Advisory Board, and the Gilead Advisory Board in Italy. Oleg Borisenko and Sun Sun are employees of Synergus AB, the Med Tech consulting company, commissioned by Sequana Medical AG to perform analysis of resource use and cost data for this clinical study. Randall Watson is an employee of Medicalwriters.com, commissioned to provide medical writing as well as scientific consulting services including data analysis and interpretation. All other authors have no disclosures.

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Author Contributions:

RJ, DA, and CB were responsible for study concept and design. RJ, CB, PA, NI, RW, CT MS, OB, SS, and ZMY were responsible for analysis, interpretation of data, and drafting and critical review of manuscript. CB, DA, MCR, LE, DV, MPR, AM, VV, MST, JC, PA, SR, SM, MM, and RJ were responsible for data acquisition.

Abstract (275 words)

Background and aims: Patients with refractory ascites (RA) require repeated large volume paracenteses (LVP), which involves frequent hospital visits and is associated with poor quality-of-life. This study assessed safety and efficacy of an automated, low-flow pump (alfapump [AP]) compared with LVP [SoC].

Methods: Randomized, controlled trial, in 7 centers, with 6M patient observation. Primary outcome was time to first LVP. Secondary outcomes included paracentesis requirement, safety, health-related quality-of-life (HRQoL), and survival. Nutrition and hemodynamics were assessed in a sub-study at 3M.

Results: 60 patients randomized and 58 were analyzed (27-AP, 31-SoC, mean age 61.9y, mean MELD 11.7). Eighteen patients were included in the sub-study. Compared with SoC, median time to first LVP was not reached after 6 months in the AP group, meaning a significant reduction in LVP requirement for the AP patients (AP, median not reached ; SoC, 15.0 days (95%CI 13.0, 22.0); HR: 0.13, $p<0.001$), and Chronic Liver Disease Questionnaire (HRQoL) score ($p<0.05$ between treatment arms). Improvements in nutritional parameters were observed for hand-grip strength ($p=0.044$) and body mass index ($p<0.001$) in the sub-study. Compared with SoC, more AP patients reported adverse events (AEs; 96.3% vs. 77.4%, $p=0.057$) and serious AEs (85.2 vs. 45.2%, $p=0.002$). AEs consisted predominantly of acute kidney injury in the immediate post-operative period, and re-intervention for pump related issues, and were treatable in most cases. Survival was similar in AP and SoC.

Conclusions: The AP system is effective in reducing need for paracentesis and improving HRQoL in cirrhotic patients with RA. Although the frequency of SAEs (and by inference

hospitalizations) were significantly higher in the AP group, they were generally limited and did not impact survival. www.clinicaltrials.gov#NCT01528410

Keywords: refractory ascites; liver cirrhosis; paracentesis

Lay Summary: The alfapump moves abdominal fluid into the bladder from where it is then removed by urination. Compared with standard treatment, the alfapump reduces the need for large volume paracentesis (manual fluid removal by needle) in patients with medically untreatable ascites. This can improve life quality for these patients.

Introduction

Accumulation of ascites is a common complication of cirrhosis and one of the leading reasons for hospital admission [1] . Approximately 60% of cirrhotic patients develop ascites within 10 years of diagnosis. Treatment of ascites includes restriction of dietary sodium and diuretics [2]. However, some patients develop diuretic-resistant or intractable ascites, because of diuretic-induced complications such as renal dysfunction, hyponatremia or hepatic encephalopathy (HE) [3, 4].

Current guidelines for the treatment of refractory ascites (RA) are large volume paracentesis (LVP) [5] with albumin infusion to decrease the risk of paracentesis-induced circulatory dysfunction (PICD) [6]. Although LVP is considered safe, it requires patient hospital contact as often as weekly and is associated with poor quality of life and malnutrition, which together increase morbidity and mortality [7, 8].

In selected patients with RA, a transjugular intrahepatic portosystemic shunt (TIPS) is a therapeutic alternative to repeated LVPs [9]. Unfortunately, TIPS is contraindicated in patients with marked pulmonary arterial hypertension, heart failure, advanced liver disease, significant hepatic encephalopathy, uncontrollable coagulopathy, and elevated right or left heart pressures [10]. Orthotopic liver transplantation is the only definitive treatment for RA, but availability is limited by organ availability, relatively low MELD scores that disadvantage RA patients on transplant waiting lists, and attendant costs [11]. Therefore, repeated LVP is the mainstay of treatment of RA.

The poor nutrition and decreased quality of life in RA patients treated with repeated LVPs, the Automated Low-Flow Ascites Pump System (alfapump® system, Sequana Medical AG, Zurich, Switzerland (Supplementary Figure 1), was developed as an alternative to LVP. The alfapump is a fully implantable, programmable, and rechargeable pump system that automatically diverts ascitic fluid from the peritoneal cavity to the urinary bladder, allowing fluid removal by micturition. The system allows remote monitoring of fluid transport and tailored therapy dependant upon ascites production. The alfapump system is intended to provide an alternative treatment for RA, which may improve HRQoL and nutrition by reducing repeated LVPs in those patients who are not candidates for TIPS. PIONEER, a prospective, open label, uncontrolled study, demonstrated the safety of the alfapump system and a significant reduction in the need for paracentesis in patients with RA. The study, however, lacked a control group [12].

The aim of this study was to perform a randomized and controlled study to evaluate the safety and efficacy of the alfapump system in cirrhotic patients with RA in comparison with LVP.

Materials and methods

Ethics

The study was approved by the ethics committees at all centers and registered on www.clinicaltrials.gov, #NCT01528410). Each patient gave written, informed consent in accordance with the principles of the Declaration of Helsinki of the World Medical Association [13]. All authors had access to the study data and reviewed and approved the final manuscript.

Definitions

Refractory ascites: Ascites that cannot be mobilized or early recurrence of which (i.e., after therapeutic paracentesis) that cannot be satisfactorily prevented by medical therapy [3].

Acute Kidney Injury (AKI): All episodes of AKI (increase in serum creatinine of 0.3 mg/dL within 48 hours, or >50% from baseline within the prior 7 d [14, 15], and renal insufficiency will be referred to as AKI.

Large Volume Paracentesis [16] : Removal of ≥5 L of ascitic fluid from the peritoneal cavity.

Paracentesis: Any therapeutic paracentesis including LVP but not including diagnostic paracentesis.

Study design and procedures

This prospective, multicenter, open-label, randomized, controlled study of patients with RA due to cirrhosis was performed at seven centers from five countries: United Kingdom, France, Austria, Spain and Italy (Supplemental Table 1). Randomised patients were followed for a nominal 180-day treatment phase, after which SoC patients were able to switch to the alfapump system study arm. An exploratory sub-study was performed on the first 18

patients enrolled at the Royal Free Hospital in London, to investigate the effects of the alfapump system on nutrition, hemodynamics and biomarkers of renal injury, after 90 d.

Paracentesis was carried out, when required, using study site standard protocols. Patients randomized to the AP arm received antibiotic prophylaxis (norfloxacin 400 mg/day or ciprofloxacin 750 mg/week) for study duration. Diuretic therapy was discontinued after implantation in all patients randomized to the AP arm, and re-started at investigator discretion if required. SoC group patients maintained their pre-study diuretic therapy regimen; changes to diuretic dosages were allowed at investigator discretion but were reduced or stopped in case of diuretic-related complications. Abstinence from alcohol and controlled salt intake were recommended for both groups throughout the study duration.

The alfapump was surgically inserted subcutaneously in the upper right quadrant of the abdomen, as described [12]. Perioperative antibiotics (ceftazidime 2 g and teicoplanin 400 mg pre-surgery and again 12 h post surgery) were recommended; deviations were allowed according to local practice. The alfapump system was activated the day after surgery. If necessary, pump parameters such as the targeted daily pump volume and the time of day during which the pump is active were adjusted during patient visits. Fluid transport by the **alfa**pump was monitored remotely. Initial pump settings were estimated from the patient's paracentesis history and subsequently modified based on patient weight and volume of ascitic fluid present.

The schedule of visits was identical for both groups after the initial 7 d and included visits at Day 7, 14, 21, 30, 60, 90, and 180. AP patients were assessed daily during the period of

hospitalization following alfapump implantation, whereas SoC patients were only seen during the first 7 days if necessary. For relevant comparison, safety is reported including and excluding the 7-day post-implant period. Albumin administration was at the discretion of the investigator and specifically indicated for (a) paracentesis, (b) spontaneous bacterial peritonitis and (c) episodes of acute kidney injury, and also for episodes of hyponatremia. Patients enrolled in the sub-study underwent additional assessments at baseline, Day 30, and Day 90.

Eligibility

Males and non-pregnant females ≥18 years old with liver cirrhosis (based upon histological features, ultrasound, or clinical signs including ascites, hepatic encephalopathy, thrombocytopenia, and splenomegaly) and RA requiring periodic LVP (≥5 L) and albumin administration [4] were included (Supplementary Table 2). Subjects also needed to demonstrate willingness to comply with study procedures, the ability to operate the device, and centers were advised not to enroll subjects eligible for TIPS. Further exclusion criteria are listed in Supplimentary table 2.

Primary endpoint was time to first LVP. Paracentesis was indicated when the patient complained of tense ascites and timing at investigator discresion. Secondary endpoints included overall paracentesis requirement, overall safety including renal injury and infections, a disease-specific health-related quality of life (HRQoL) instrument (chronic liver disease questionnaire (CLDQ)), and survival. Surgical, anesthetic and device-related complications in the treatment group were measured. Economic outcomes included

number and cost of study visits, paracentesis visits, AE related visits and hospitalizations, over 6 months. In the sub-study, nutritional status including BMI, hand grip, mid-arm muscle circumference (MAMC), triceps skin fold thickness (TSF), and the Royal Free Hospital General Assessment (RFH-GA) [17] were measured. Additionally, hemodynamic markers and biomarkers of renal injury including cardiac index, systemic vascular resistance, plasma renin activity, kidney injury molecule-1 (KIM-1) and urinary neutrophil gelatinase-associated lipocalin (NGAL) were measured for sub-study patients.

Statistics and sample size

Patients were randomized to either the alfapump system group (treatment group AP) or LVP group (treatment group SoC) by a centralized, computer-generated method to achieve a 1:1 ratio. Over 6 months, 71% of AP patients are expected to require LVP [12]. Conservatively estimating 97% of SoC patients require LVP over 6 months equates to a hazard ratio (SoC:AP) of 2.83 [18]. Based on the assumption of proportional hazards, a log-rank test of equality of survival distributions, with a 5% two-sided significance level and 90% power requires 23 LVP events per group, requiring a sample size equivalent to 28 patients per group and 56 in total.

Analyses were carried out using SPSS Version 23.0, SAS Version 9.3 or higher, and R version 3.2.2. Descriptive analysis was performed for all primary and secondary variables. Continuous variables were described with means, medians, standard deviation, 95% confidence interval, minimum and maximum values of each distribution, and interquartile range (IQR). Categorical variables were described using frequencies and percentage of patients in each category.

Time to LVP and survival time were compared using Kaplan-Meier estimators and log-rank tests. Other parameters were compared using appropriate methods depending on the type.

HRQoL data were systematically collected for study participants at baseline, 1-, 2-, 3- and 6-months' time points. The QoL scores were compared between the treatment arms using a non-parametric rank sum test, and to patients' own baseline levels using a sign rank test.

Economic analysis

A within-trial economic analysis was performed using a bottom-up approach [19], and from the perspective of the National Health-Care System (NHS) in the UK. Only direct costs were included as follows: costs for alfapump implantation , costs of LVP, costs of typical management of ascites (laboratory tests, medications, scheduled visits), and costs related to AE treatment. For analysis of resource use and AEs costs: the AE category was determined using data on hospitalization requirement, elective vs. non-elective admission, diagnosis, and provided treatment; events were grouped for a single patient if they were reported during the same admission or out-patient visits, payment mechanism and costs were estimated for groups of events or individual events.

For cost estimates of treatment in each treatment arm, quantities of resource use were multiplied by their corresponding unit costs. Pharmaceuticals costs were estimated using British National Formulary [20], Drugs and Pharmaceutical Electronic Market Information Tool [21] and National Health Services Drug Tariff for England and Wales [22].Cost of physician/nurse visits was estimated using data from Personal Social Services Research Unit [23] and cost of hospital and out-patient specialist care was based on UK Departments' of

Health NHS Reference cost [24]. All costs were presented using 2015/2016 British Pounds. Inflation adjustments were made using Hospital & Community Health Services index.
For descriptive analyses for resource use and costs, median and interquartile range were used, Mann-Whitney U test was used for comparison between groups.

Sub-Study

The sub-study was designed to provide descriptive data and assess the effect of the alfapump on the measured parameters. A power calculation was not possible, as no prior data existed. A sample size of 18 patients (1:1 ratio AP versus SoC) was sufficient for the exploratory objectives of the sub-study.
The data were interpreted using an analysis of covariance using the baseline measure as the covariate. Plasma renin values were log10 transformed for analysis. Nutritional data were on an ordinal scale, whereby the three categories were ordered. These data were analyzed by the Cochran-Mantel-Haenszel procedure. The one and three-month data were stratified by their baseline category. The three ordered categories were assumed to be equally spaced.

Results

Baseline Characteristics and Patient Disposition

Between July 2012 and February 2015, 216 potential patients were pre-screened, and 81 patients signed informed consent. Most commonly unmet inclusion/exclusion criteria were; significantly decreased life expectancy or high anesthetic risk (comorbidity) (8.3%), unwilling to give consent (7.4%) no refractory ascites requiring LVP (6.5%), renal failure (6.5%), death

before enrolment (5.6%), or advanced hepatocarcinoma (5.1%). Of the 81 consented patients, 60 patients met ultimate eligibility criteria and were randomized (screening and exclusion summary given in Supplemental Table 2) and constitute the intent-to-treat (ITT) population. Following randomization, 29 were allocated to the alfapump system treatment arm (AP) and 31 to the LVP standard of care (SoC) control arm. Ultimately, 58 patients – 27 patients in the AP group and 31 patients in the SoC group – received the designated treatment and constitute the safety population. Of these 58 patients, 17/27 (63%) in the AP group and 21/31 (68%) in the SoC group completed the study, and 10 from each study arm withdrew due to serious adverse events (SAEs), death, or other reasons. Median time on study was equivalent in both groups and details are provided in the CONSORT diagram (Figure 1).

Baseline characteristics and patient demographics were well-balanced, with no significant differences between the two treatment groups (Table 1). The mean age of patients in the AP group was 61.1±8.5 years vs. 62.6±8.4 years in the SoC group. In both groups, approximately 80% of patients were male, mean MELD scores were 12.2±2.5 and 11.3±3.9, and mean Child-Pugh scores of 8.2±1.1 and 8.4±1.1 for the AP and SoC groups, respectively. Most patients in both groups were Child-Pugh Class B and alcohol was the most common etiology of cirrhosis. Median time since the requirement for paracentesis was 1.1 (IQR 1, 2) and 1.0 years (IQR 1, 2) in the AP and SoC groups, respectively. Previous hospitalization (within 3 months of study entry) for a cirrhosis complication occurred in 52% of AP and 68% of SoC group patients and contraindications to TIPS included coronary artery disease/heart failure, hepatic encephalopathy, non-functioning TIPS, portal vein thrombosis, pulmonary hypertension, anticoagulation, and patient discretion.

Sub-study: The first 18 eligible patients at RFH were randomized to the sub-study and of these, 16 patients were included in the final analysis, eight in each group. One patient developed urinary retention before pump insertion and was withdrawn in the AP group, and one withdrew consent in the SoC group. Patient characteristics and demographic baseline data including the median age of patients, etiology of cirrhosis and the MELD scores were similar as shown in Table 1.

Implant Procedure and Antibiotic Prophylaxis

In the AP group, 96.3% (26/27) patients received primary or secondary antibiotic prophylaxis for spontaneous bacterial peritonitis versus 80.6% (25/31) in the SoC group. Mean duration of implant procedure was 65.0 ± 20.6 min (min. 30, max. 130), all were performed under general anesthesia (12 laparoscopically [44.4%], 15 open [55.6%]).

Efficacy

Time to first LVP was significantly greater in the AP group compared with SoC (HR: 0.13, $p<0.001$; Figure 2). The median number of LVP was significantly higher in the SoC group compared with the AP group wherein median time to first LVP was not reached after 6 months (risk ratio SoC/AP [CI]: 7.7 [3.6 to 16.7] $p<0.001$) as was the median number of events/patient as shown in Figure 2. Of the total number of LVP events, 90% occurred in the SoC group.

LVP was required in 90% (28 patients) of the SoC group and 37% (10 patients) of the AP group. Of those in the AP group that required LVP, 4 patients accounted for 68% of all

paracenteses, the causes of which are listed in Supplemental Table 3. One AP group patient had the pump removed on Day 8 due to infection and required 7 post-explant LVPs.

Health-related quality of life (Chronic Liver Disease Questionnaire)

The disease-specific instrument, Chronic Liver Disease Questionnaire (CLDQ) was used to measure health-related quality of life (HRQoL) [25]. The Abdominal Symptoms and Activity scores improved significantly only in RA patients treated with alfapump ($p<0.05$ both when compared to baseline and between treatment arms). The average improvements in score after 3 months of treatment with alfapump were +1.25 and +0.80, respectively, on a 1-7 scale; notably, these improvements were sustained in AP group patients for months and substantially exceed the thresholds of clinical importance [26]. At the same time, no significant improvement in any HRQoL scores was observed in SoC group patients (Figure 3). Changes in QoL were not significantly different at 6 months.

Nutrition

Using the RFA-GA tool in the sub-study, improvement in nutritional status from baseline to Day 90 was seen in 4/8 (50%) patients in the AP group and none of the SoC group. In the 4 patients who improved in the AP group, 3/4 improved within 30 days and 1 improved after 90 days. In the AP group, 5/8 (63%) patients were “adequately nourished” at 90 days versus only 3/9 (33%) in the SoC group, and only 1 (13%) patient in the AP group did not complete 90 days versus 3 (33%) in the SoC group. Overall, there was a trend to improved nutritional status in the AP group compared with SoC ($p=0.099$ at Day 30 and $p=0.090$ at Day 90. Nutritional parameters are shown in Table 2. Compared with the SoC group, there were

statistically significant improvements seen in body mass index (BMI), mid-arm muscle circumference, tricipital skin fold thickness, and hand grip strength in the AP group.

Health economic analysis

Median number of out-patient visits (3 [IQR 2, 9] vs 2 [IQR 1, 3.8] in SoC group, p<0.001) and hospitalizations (2 [IQR 2, 4] vs 1 [IQR 0.25, 1.5], p<0.001) due to adverse events (AEs) was higher in AP group compared with SoC group at 6 months. A total and breakdown of costs is provided in Supplementary Table 10. Total median cost of (0-180 days), including implantation procedure and device, scheduled visits, lab test, medications and treatment of adverse events was significantly higher in AP group (£36970 [IQR 29910, 46850]) relative to SoC group (£12660 [IQR 7972, 18100], p<0.0001). The difference is primarily due to the statistically higher cost of implantation procedure (including cost of the device) (£22230 [IQR 21560, 23630] vs. £0 respectively, p<0.001) and AE events (£3983 [IQR 1789, 9432] vs. £1504 [IQR 2, 5126] for AP vs. SoC respectively, p=0.002) . The cost of paracentesis was statistically higher in SoC group compared with AP group (£7254 [IQR 3711, 13550] vs £1682 [IQR 0-3796], p<0.001). For post 3 month (1-90 days), AP group had significantly higher cost for scheduled visits, AE events and lab test relative to SoC group, but significantly lower cost for paracentesis relative to SoC group (p<0.0001). For post 3-6 month (91-180 days), the AP group had significantly lower cost for paracentesis relative to SoC group (p<0.0001). No significant differences were found for any other cost items between the two groups. There was no significant trend towards higher cost for the period of 1-90 days post-implantation (excluding cost of implantation procedure and device) in AP group vs SoC group (£1496 [IQR 1360-1496] vs £952 [816-1088] respectively, p=0.181) and lower total cost for the period of 91-180 days (£1704 [IQR 308-3574] vs £3265 [328-6613] respectively, p=0.348).

Safety

More patients in the AP group had at least one treatment-emergent adverse event (TEAE) than in the SoC group (96.3% versus 77.4%, p=0.057) and there were approximately twice as many in the AP group (199) compared with the SoC group (97) or 7.4 and 3.1 per patient, respectively. Compared with SoC, approximately twice as many AP patients had serious TEAEs (85.2% versus 45.2%, p=0.002) and there were 64 serious TEAEs in the AP group and 27 in the SoC group, or 2.4 and 0.9 per patient, respectively, as noted in Table 3.

Of serious TEAEs, there were statistically more AP group patients with nervous system disorders (2 with hepatic encephalopathy, the others related to electrolyte abnormalities, alcohol withdrawal, and stroke; p=0.042), and renal and urinary disorders (p<0.001). Procedural complications were observed in the AP patients and these are summarised in Table 3.

Survival

There was no significant difference in overall survival (including off-treatment) between the AP and SoC groups (p=0.355) as shown in Supplementary Figure 2. Six patients in the alfapump group and 4 patients in the SoC arm died during the 6-month study period. One death in the AP group occurred shortly after withdrawl from the study (still within 6 months) following recovery from pump explant for infection. Causes of death are consistent with advanced liver disease and are shown in Supplemental Table 4.

Infection

TEAEs due to infection are shown in detail in Supplemental Table 5. Twenty-five patients in the AP group suffered treatment emergent infections with 23 fully recovering, 1 recovered with sequelae, and 1 deceased (sepsis), compared with 30 infections in the SoC group wherein 26 fully recovered, 3 were ongoing or outcome was unknown, and 1 deceased (SBP). Specifically, the incidences of spontaneous bacterial peritonitis and urinary tract infections were similar. The nature and frequency of patients with SAEs due to infection were similar in each group (p=0.883) as can be seen in Supplementary Table 5 and Table 3 (SAE by outcome section) .

Circulatory dysfunction

Acute kidney injury

More than 50% of the AP group patients experienced SAEs related to the renal and urinary system. Except for 3 patients with hematuria and urethral stenosis, the others were due to AKI. Just over 41% of these AEs in the AP group (12/29) occurred in the first 7 days after implant and were transient, and of those 10/12 fully recovered and 2/12 improved (Supplemental Table 6). There were significantly more AKI events in the AP group than in the SoC group (29 vs. 11, respectively; p=0.007). If the first 7 post-operative days are excluded, there were similar numbers in each group (17 vs. 11, respectively; p=0.281, Table 3). One patient in the AP group with alcoholic liver disease and a history of hepatic encephalopathy died of end-stage liver disease and liver failure 52 days after implantation. This was caused by septic shock and consequent AKI that occurred on the background of a severely infected diabetic foot requiring amputation.

Serum creatinine

There was no significant change from baseline in creatinine levels between or within groups at any time point. The means, medians and interquartile ranges (IQR) of changes in serum creatinine are shown in Supplementary Table 9.

Serum albumin

The fall in albumin (g/L) over time was significantly greater in the AP group than SoC at Days 60, 90, and 180 (Supplementary Table 9). The AP group received significantly less total albumin after Day 0 over the course of the study than the SoC group (Supplementary Figure 5) and in the AP group, albumin was administered predominantly for renal insufficiency. In addition to infusion during LVP, albumin was administered in the SoC group for similar reasons.

Hyponatremia

There were 7 hyponatremia-related AEs in 5 patients in the AP group, 3 of which required hospital admission and all occurred > 7 days after the implant. There were 3 hyponatremia AEs in 3 patients in the SoC group, one of which required hospitalisation and all occurred > 7 days after randomization. Each of these episodes was readily corrected with fluid restriction and/or volume resuscitation.

Hemodynamics, plasma renin activity, and inflammatory biomarkers including markers of kidney injury

In the sub-study, no significant changes were noted in cardiac index, mean arterial pressure, heart rate, stroke volume, or plasma B-type natriuretic peptide. A trend was noted suggesting an increase in both systemic vascular resistance (SVR, p=0.129) and plasma renin

activity (p=0.144) at 3 months but not at 1 month. A statistically significant rise in NGAL was noted at 3 months (p=0.043) but no significant differences were noted for kidney injury molecule-1 (KIM-1), tumor necrosis factor, IL6, IL1β, white cell count, or C-reactive protein. These are shown in Supplemental Tables 7 and 8.

Reinterventions

Of the 27 AP group patients, 12 patients were reported with at least one device deficiency, 7 patients required reintervention due to device deficiency, 6 (22%) required system component replacement or repositioning and 3 (11%) required system explant as detailed in Table 4. All fully recovered. No patients discontinued the study due to device deficiency. Of the 17 patients who completed the study, 11 did so without pump system reintervention although 2 required replacement chargers, and 7 of 10 patients who withdrew or died did so inspite of fully functioning pump system (although 1 required charger replacement and 2 required pump system explant due to pump pocket infection). Overall 66.6% of implanted systems functioned without reintervention until study completion, withdrawal or death.

Discussion

This study is the first randomized, controlled clinical trial that investigates the safety and efficacy of the alfapump system to treat RA compared with a control cohort managed with LVP. The data add to the existing body of evidence confirming that the alfapump system is efficacious in reducing, and in many cases eliminating, the need for paracentesis. This reduction was associated with significant improvements in HRQoL and nutrition. Although the total number of infectious complications was similar between groups, there were

significantly more AKI events in the AP patients, the overall outcomes from which were not different between the groups.

The alfapump system is designed to obviate the need for paracentesis and successfully eliminated the need for LVP in more than 50% of implanted patients over 6 months. The majority of necessary LVPs were attributable to catheter blockage or migration and this remains an area of potential improvement in device design. Renal dysfunction, resulting in the decision to reduce the programmed rate of daily fluid transport in 2 patients, was also a contributing factor and may also be an area where device programming and peri-implant care protocols including albumin administration may be desirable.

Although there was no significant difference between groups in the number of AEs related to AKI and hyponatremia occurring >7 days after implantation, more of these events required hospitalization in the AP group. The underlying mechanism for this renal dysfunction and hyponatremia remains unclear and may be related to gradual albumin depletion, resulting in circulatory dysfunction as evidenced by an increase in plasma renin activity. Recently reported haemodynamic observations, correlated to alfapump treatment, are hypothesised to indicate treatment-related change in effective arterial blood volume, which mimics postparacentesis circulatory dysfunction syndrome [27]. The events occurring within the first seven days following implant may also be related to sterile inflammation induced by the surgical procedure or related to manipulation of the abdominal wall and rapidly changing abdominal pressures, or both. It is also possible that prophylactic perisurgical administration of albumin may help prevent these transient episodes of AKI and electrolyte imbalance, a point also noted by Sola *et al*.[27] However, it is important to note

that despite the lack of albumin substitution and significant reduction in albumin levels in the AP group, there was no significant difference in change from baseline in creatinine, number of patients with infection, or overall survival between groups.

The QoL data collected during this study show a marked improvement in QoL scores, especially in the first 3 months of treatment. This is important because patients with advanced liver disease and RA suffer from very marked impairment of QoL. This increase in QoL reflects significant improvement of patients' experience with their liver disease. Nevertheless, it is important to note that patients with refractory ascites generally have high 6-month mortality. Furthermore, a number of these patients are expected to receive liver transplants. In this context, the number of patients who remained in the study and completed QoL questionnaires at the later study time points was limited, dampening the power of the study and statistical significance of QoL score improvements.

Implantation of the alfapump system was associated with improvements in nutritional status compared with the SoC group measured by improved BMI, hand grip, TSF and MMAC, compared with the LVP group. Due to the small number of patients evaluable at 6-months and the design of the sub-study, it remains unclear if these nutritional benefits extend for periods longer than 3-months. Additionally, the mechanism by which this nutritional benefit occurs is unknown but may involve attenuation of the increased resting energy expenditure associated with ascites [28].The improvements noted were similar to the improvements in body composition and resting energy expenditure seen following TIPS insertion [29, 30].

Three pumps were explanted due to pump pocket issues such as infection or wound dehiscence. Clearly, wound infection or dehiscence limits the utility of the alfapump system and is problematic in patients with decompensated cirrhosis who are generally compromised with poor wound healing. Device deficiencies accounted for 7 re-interventions and no patients discontinued for this reason. This is an improvement compared to the results of the PIONEER study and may reflect the continual technological improvements to the alfapump system since commercialization in 2011.

Despite higher implantation cost for alfapump (£22,230), for the post-intervention cost, in AP group there was a trend towards stabilized costs, while in SoC group there was a steady increase mainly caused by high costs of paracentesis. Further improvements for the Alfapump in surgical protocols, post-implant care procedures, and system configuration e.g. catheter design, antibiotic coatings, and pump shape may help to reduce the cost for AP, and improve the cost-effectiveness of the alfapump. Further investigations with longer follow-up time are needed, to better understand the economic value of AP.

In conclusion, results of this study show that the alfapump system was effective in significantly reducing the need for paracentesis and improving HRQoL in those with refractory ascites due to cirrhosis and improved overall nutrition in a non-selected subset of those patients. Although SAEs were more common in the AP group these were generally limited and did not affect overall survival at 6 months. The impact of refinements in patient selection, patient care algorithms - including regular albumin administration to reduce the risk of circulatory dysfunction and infection - as well as modifications in device design remain areas for future study.

Acknowledgements

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Compensated Liver Disease, Including Cirrhosis 2014 [cited 2016 2 Dec]; Available from: http://www.ncbi.nlm.nih.gov/books/NBK253697/.

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Figure legends:

Figure 1. CONSORT flow diagram of patient enrollment, allocation, follow-up, and analysis.

Figure 2. A, Kaplan-Meier plot comparing the time until the first large volume paracentesis (LVP) between alfapump group patients and standard of care LVP–treated patients. P values from log-rank test; Hazard ratio from Cox proportional hazards regression model. **B and C**, Box and whisker plots of mean and median paracentesis and LVP per patient, and per patient per 28 day month, for the AP (blue) and SoC (red) patient groups. The solid circles inside the box and numbers inside or above the box are the means, the horizontal bar inside the box (red) and forming the bottom of the box (blue) are the medians, as denoted by the number beside the box. Upper and lower quartiles are indicated by the upper and lower extent of the box and the extremes represented by the whiskers. Significant differences between AP and SoC for all measures noted, $p<0.001$ determined by two-sided t-test. **D**, Cumulative incidence of LVP and paracentesis events, with number at risk through time. Per protocol, patients were considered to complete the study after their 6-month visit at Day 180 ± 20. One patient in the SoC group completed the study on Day 234 with last recorded paracentesis on Day 119. Paracentesis is defined as any needle stick paracentesis for the purpose of ascites removal (not sampling) after Day 0 until withdrawal or completion. LVP defined as any paracentesis (as above) of 5 L or more. Significant differences between AP and SoC for both AP and SoC noted, $p<0.001$ (two-sided t-test)

Figure 3. Prospectively collected HRQoL Chronic Liver Disease Questionnaire (CLDQ) abdominal and activity scores by the treatment arm. Both scores significantly higher in the AP group as compared to the SoC group when compared to baseline and between treatment arms ($p<0.05$; two-sided t-test).

Table Headings:

Table 1. Baseline demographic and clinical characteristics

Table 2. Nutritional parameters

Table 3. Treatment emergent adverse events and treatment emergent serious adverse events.

Table 4. Reinterventions

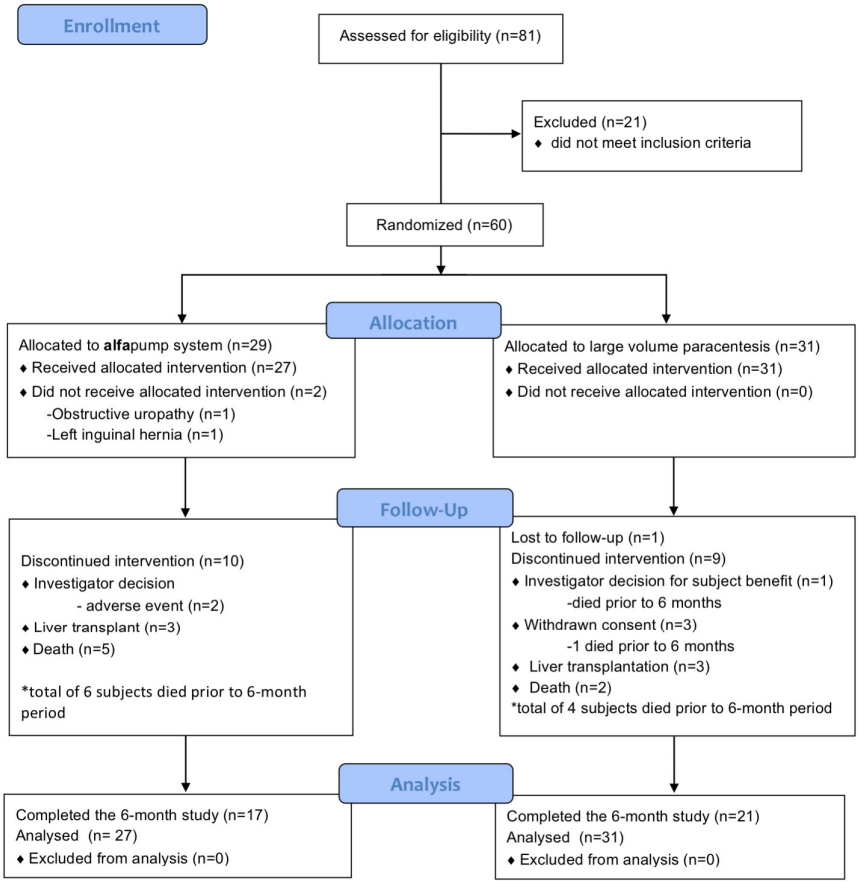
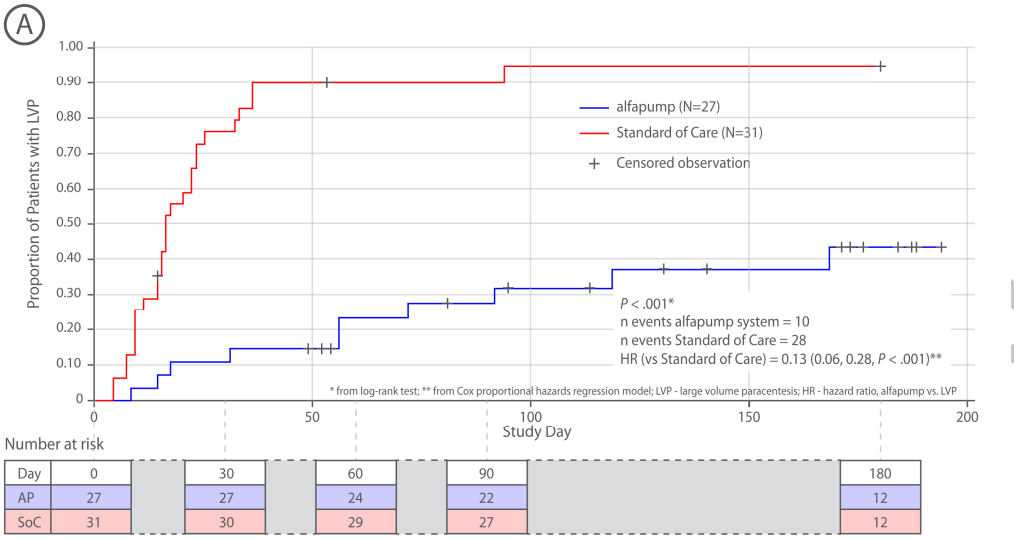
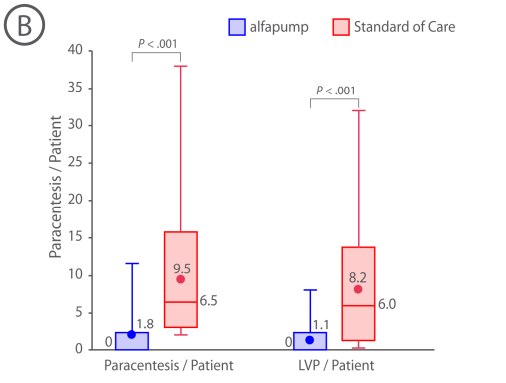


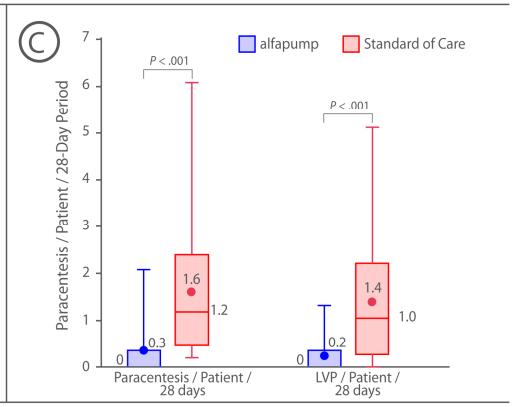
Figure 1. CONSORT flow diagram of patient enrollment, allocation, follow-up, and analysis.

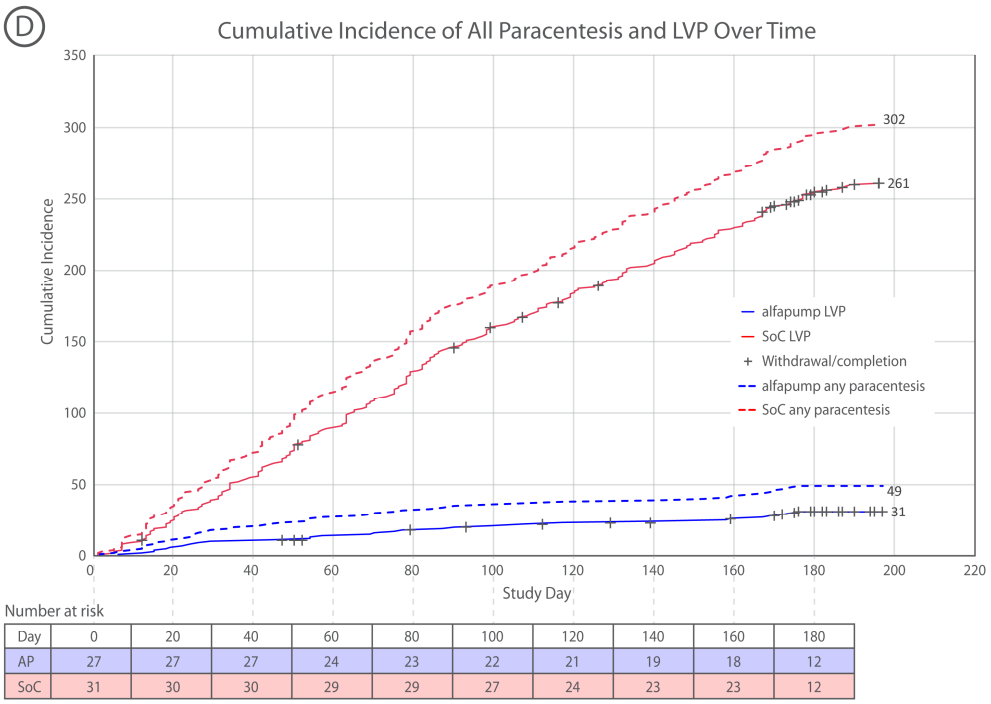


Number at risk

Day	0	30	60	90	180
AP	27	27	24	22	12
SoC	31	30	29	27	12



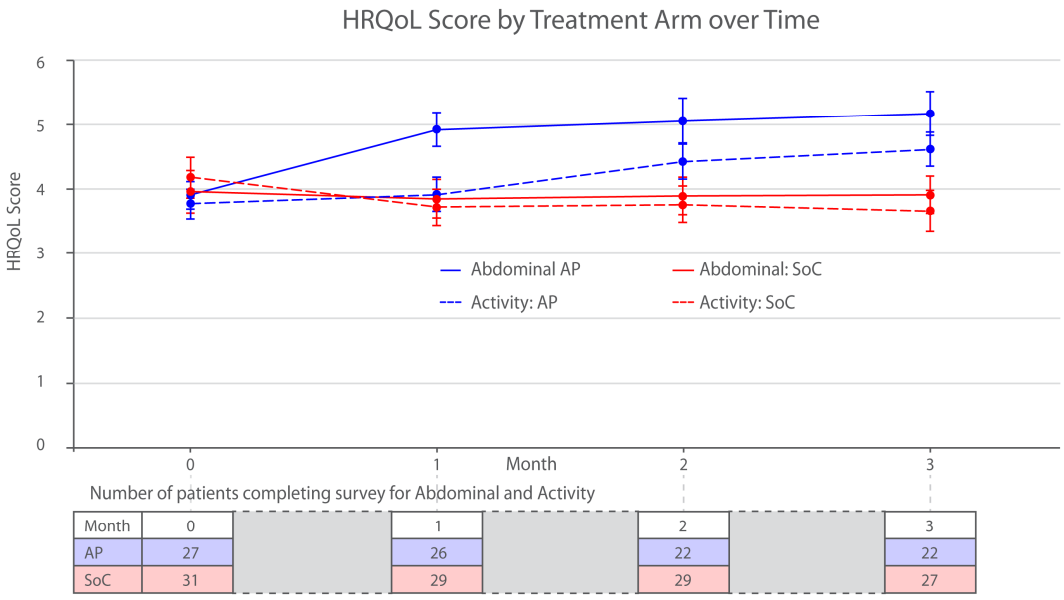




Number at risk

Day	0	20	40	60	80	100	120	140	160	180
AP	27	27	27	24	23	22	21	19	18	12
SoC	31	30	30	29	29	27	24	23	23	12

Figure 2



Number of patients completing survey for Abdominal and Activity

Month	0	1	2	3
AP	27	26	22	22
SoC	31	29	29	27

Figure 3

Table 1. Baseline characteristics

	AP N=27	SoC N=31	P-value†	Substudy N=16	Not in Substudy N=42	P-value†
Age (years), mean (SD)	61.1 (8.5)	62.6 (8.4)	0.537	62.3 (7.5)	61.8 (8.8)	0.787
Gender (male), n (%)	21 (77.8%)	25 (80.6%)	1	12 (75.0%)	34 (81.0%)	0.720
BMI (kg/m²), mean (SD)	27.7 (4.8)	27.3 (5.7)	0.596	26.8 (4.5)	27.8 (5.6)	0.676
MELD Score, mean (SD)	12.2 (2.5)	11.3 (3.9)	0.121	12.8 (3.9)	11.5 (2.9)	0.438
Child-Pugh score, mean (SD)	8.2 (1.1)	8.4 (1.1)	0.78	8.1 (1.3)	8.4 (1.0)	0.341
Child Pugh Class, n (%)			0.855			0.975
B	22 (81.5%)	24 (77.4%)		13/15 (86.7%)	33/39 (84.6%)	
C	3 (11.1%)	5 (16.1%)		2/15 (13.3%)	6/39 (15.4%)	
Etiology of Liver Cirrhosis, n (%)						
Alcohol	20 (74.1%)	21 (67.7%)	0.773	9 (56.3%)	32 (76.2%)	0.197
Non-alcohol	7 (25.9%)	10 (32.3%)		7 (43.8%)	10 (23.8%)	
Time since start of paracentesis treatment (years), mean (SD)	1.1 (1, 2)	1.0 (1, 2)	0.397	1.1 (0.8)	1.6 (1.7)	0.670
Platelets, 10^9/L mean (SD)	135 (78)	138 (53)	0.887	116 (47)	148 (73)	0.142
Albumin, g/L mean (SD)	33.7 (6.1)	31.0 (5.2)	0.075	35.1 (6.0)	31.4 (5.6)	0.022
History prior to enrolment						
Renal failure, n	11 (40.7%)	6 (19.4%)	0.163	9 (56.3%)	9 (21.4%)	0.024
Hepatorenal syndrome, n	3 (11.1%0	4 (12.9%)	1.000	3 (18.8%)	5 (12.2%)	0.673
Hepatic encephalopathy, n	8 (29.6%)	9 (29.0%)	0.784	6 (37.5%)	12 (29.3%)	0.545
Spontaneous bacterial peritonitis, n	7 (25.9%)	7 (22.6%)	0.764	4 (25.0%)	10 (24.4%)	1.000
Urinary infection, n	1 (3.7%)	3 (9.7%)	0.617	0 (0%)	4 (9.8%)	0.568
Variceal haemorrhage, n	11 (40.7%)	6 (19.4%)	0.090	6 (37.5%)	11 (26.2%)	0.520
Hospitalized in previous 3 months, n (%)*	14 (52%)	21 (68%)	0.285	15 (93.8%)	20 (47.6%)	0.002
Contraindications to TIPS, n (%)	**AP N=27**	**SoC N=31**				
Coronary artery disease / heart failure	4 (14.8%)	6 (19.4%)	-	-	-	-
Hepatic encephalopathy	9 (33.3%)	9 (29.0%)	-	-	-	-
Non-functioning TIPS	1 (3.7%)	2 (6.5%)	-	-	-	-
Portal vein thrombosis	2 (7.4%)	-	-	-	-	-
Pulmonary hypertension	-	1 (3.2%)	-	-	-	-
Anticoagulated	1 (3.7%)	-	-	-	-	-
Child-Pugh Class C	3 (11.1%)	5 (16.1%)	-	-	-	
Unknown**	9 (33.3%)	11 (35.5%)	-	-	-	-
Time on study (days), mean (SD)	174 (59)	184 (47)	0.431	174 (66)	181 (47)	0.379

*all overnight hospitalizations in both groups due to liver disease including those for paracenteses, spontaneous bacterial peritonitis, and TIPS and transplant evaluations
**investigator or patient choice
AP, alfapump system; SoC, Standard of Care; SD, standard deviation; TIPS, transjugular intrahepatic portosystemic shunt. †All p-values Chi-Square test except Mann-Whitney U (Age, BMI, MELD, Child-Pugh score, time since start of paracentesis, and time on study)

Table 2. Nutritional parameters

Parameter		Baseline		Day 30		Day 90	
		AP	SoC	AP	SoC	AP	SoC
Royal Free Hospital General Assessment, n (%)							
	Adequately Nourished	2 (25.0)	4 (50.0)	4 (50.0)	4 (50.0)	4 (66.7)	3 (50.0)
	Moderately Malnourished	5 (62.5)	2 (25.0)	4 (50.0)	2 (25.0)	2 (33.3)	1 (16.7)
	Severely Malnourished	1 (12.5)	2 (25.0)	0 (0)	2 (25.0)	0 (0)	2 (33.3)
	P-Value*	-		0.099		0.090	
BMI (kg/m^2)	N			7	8	6	7
	Adjusted change[1]	-	-	1.237	-0.145	1.992	-0.650
	P-Value	-		0.056		<0.001	
TSF (mm)	N			7	8	6	6
	Adjusted change[1]	-	-	0.466	-0.432	1.898	-0.848
	P-Value	-		0.137		0.003	
MAMC (cm)	N			7	8	6	6
	Adjusted change[1]	-	-	0.89	-0.24	1.80	0.16
	P-Value	-		0.010		0.008	
Hand-grip (kg)	N			7	8	6	6
	Adjusted change[1]	-	-	2.44	0.84	4.03	-1.69
	P-Value	-		0.447		0.044	

*Nourishment data were on an ordinal scale, whereby the three categories were ordered. These data were analyzed by the Cochran-Mantel-Haenszel procedure, in which the one- and three-month data were stratified by their baseline category. For the analysis, the three ordered categories were assumed to be equally spaced.

[1] Mean change from baseline adjusted for the baseline mean by an analysis of covariance

AP, alfapump system; SoC, Standard of Care; BMI, body mass index, TSF, tricipital skin fold thickness;
MAMC, mid arm muscle circumference

Table 3. Treatment emergent adverse events and treatment emergent serious adverse events

Treatment emergent adverse events (TEAE)	All			≤ 7 days			> 7 days		
	AP N=27	SoC N=31	P-value	AP	SoC	P-value	AP	SoC	P-value
Patients with at least one TEAE, n (%)	26 (96.3)	24 (77.4)	0.057	22 (81.5)	9 (29.0)	<0.001	26 (96.3)	24 (77.4)	0.057
Total number of TEAEs, n	199	97		50	10		149	87	
Average number of TEAEs/patient, n	7.4	3.1		1.9	0.3		5.5	2.8	
Patients with at least one serious TEAE, n (%)	23 (85.2)	14 (45.2)	0.002	9 (33.3)	1 (3.2)	0.004	23 (85.2)	13 (41.9)	0.001
Number of serious TEAEs, n	64	27		NA	NA		NA	NA	
Average number of serious TEAEs/patient, n	2.4	0.9		NA	NA		NA	NA	
Summary of Patients w. Treatment Emergent SAEs, n (%)	AP N=27	SoC N=31	P-value	AP	SoC	P-value	AP	SoC	P-value
Blood and lymphatic system disorders, n (%)	1 (3.7)	0	0.466	0	0	1.0	1 (3.7)	0	0.466
Cardiac disorders, n (%)	0	1 (3.2)	1.0	0	0	1.0	0	1 (3.2)	1.0
Gastrointestinal disorders, n (%)	7 (25.9)	2 (6.5)	0.068	1 (3.7)	0	0.466	6 (22.2)	2 (6.5)	0.129
General disorders and administration site conditions, n (%)	4 (14.8)	1 (3.2)	0.173	0	0	1.0	4 (14.8)	1 (3.2)	0.173
Hepatobiliary disorders, n (%)	4 (14.8)	3 (9.7)	0.694	0	0	1.0	4 (14.8)	3 (9.7)	0.694
Infections and infestations, n (%)	9 (33.3)	8 (25.8)	0.574	2 (7.4)	1 (3.2)	0.593	0	0	1.0
Injury, poisoning and procedural complications, n (%)	3 (11.1)	0	0.095	3 (11.1)	0	0.095	0	0	1.0
Investigations, n (%)	0	1 (3.2)	1.0	0	0	1.0	0	1 (3.2)	1.0
Metabolism and nutrition disorders, n (%)	4 (14.8)	1 (3.2)	0.173	0	0	1.0	4 (14.8)	1 (3.2)	0.173
Nervous system disorders, n (%)	6 (22.2)	1 (3.2)	0.042	0	0	1.0	6 (22.2)	1 (3.2)	0.042
Psychiatric disorders, n (%)	1 (3.7)	0	0.466	1 (3.7)	0	0.466	0	0	1.0
Renal and urinary disorders, n (%)	14 (51.9)	3 (9.7)	<0.001	4 (14.8)	0	0.041	10 (37.0)	3 (9.7)	0.025
Respiratory, thoracic and mediastinal disorders, n (%)	1 (3.7)	0	0.466	0	0	1.0	1 (3.7)	0	0.466

Counting is on a per-patient basis AP, alfapump system; SoC, Standard of Care; SAE, serious Adverse Event

Summary of Treatment Emergent Serious Adverse Events, by Outcome and System Organ Class n	**Outcome**						
Alfapump group (n=27)	Total	FR	RS	OI	OU	OW	DI
Injury, poisoning and procedural complications	3	3	-	-	-	-	-
General disorders and administration site conditions	4	3	-	1	-	-	-
Renal and urinary disorders	19	12	1	3	1	1	1
Gastrointestinal disorders	8	7	-	1	-	-	-
Infections and infestations	13	12	-	-	-	-	1
Metabolism and nutrition disorders	4	3	-	1	-	-	-
Hepatobiliary disorders	4	-	1	1	-	-	2
Respiratory, thoracic and mediastinal disorders	1	-	-	-	-	-	1
Psychiatric disorders	1	1	-	-	-	-	-
Nervous system disorders	6	5	-	-	1	-	-
Blood and lymphatic system disorders	1	-	-	-	1	-	-
Standard of Care Group (n=31)							
General disorders and administration site conditions	1	1	-	-	-	-	-

Renal and urinary disorders	3	2	-	1	-	-	-
Gastrointestinal disorders	2	1	1	-	-	-	-
Infections and infestations	13	12	-	-	-	-	1
Metabolism and nutrition disorders	2	-	2	-	-	-	-
Hepatobiliary disorders	3	-	-	-	1	-	2
Nervous system disorders	1	-	-	1	-	-	-
Cardiac Disorders	1	-	-	-	-	-	1
Investigations	1	1	-	-	-	-	-

Counting is per event. FR = Fully recovered, RS = Recovered with sequelae, OI = Ongoing - Improved, OU = Ongoing - Unchanged, OW = Ongoing - Worsened, DI = Died.

Summaries of Acute Kidney injury and Infectious events	AKI† All		AKI† >7 days after implant		Infection	
	AP N=27	SoC N=31	AP	SoC	AP	SoC
Total Events	30	11	17	11	25	30
Events per patient, mean	1.07	0.35	0.63	0.35	1.07	0.35
Events per patient, range	0 – 3	0 – 5	0 – 3	0 – 5	0 – 3	0 – 4
P value	0.007		0.281		0.883	

* analyzed by t-test for equality of means
†acute kidney injury or renal insufficiency or hepatorenal syndrome
AP, alfapump system; SoC, Standard of Care

	AKI† All		AKI† >7 days after implant		Infection	
	AP N=27	SoC N=31	AP	SoC	AP	SoC
Total Events	30	11	17	11	25	30
Events/Patient						
Mean	1.07	0.35	0.63	0.35	0.93	0.97
Range	0 – 3	0 – 5	0 – 3	0 – 5	0 – 3	0 – 4
P-Value*	0.007		0.281		0.883	

* analyzed by t-test for equality of means
†acute kidney injury or renal insufficiency or hepatorenal syndrome
AP, alfapump system; SoC, Standard of Care

Table 4. Reinterventions

Issue	Time to re-intervention (days)*	Intervention	Anesthesia / Type	Outcome
alfapump				
Lack of communication pump and charger	94	Pump exchange	General / Open	FR
Bladder catheter (BC)				
Kinked	5	BC repositioned and pump exchange†	General / Laparoscopy	FR
Dislocated	20	BC exchange	Local / Laparoscopy	FR
Dislocated	113	BC exchange	Local / Interventional radiology	FR
Peritoneal catheter (PC)				
Disconnected	6	PC and BC repositioned and pump exchange†	Local / Open	FR
Dislocated and occluded	177	PC and pump exchange†	General / Open	FR
alfapump system (AP)				
SBP / cellulitis / UTI	8	System explant	Unknown	FR
Pocket hematoma / abscess	50	System explant	General / Laparoscopy	FR
UTI /pocket abscess / wound dehiscence /	79	System explant	General / Laparoscopy	FR

FR, fully recovered; UTI, urinary tract infection; SBP, spontaneous bacterial peritonitis; BC, bladder catheter; PC, peritoneal catheter
*prophylactic pump exchanges performed at time of catheter re-interventions due to failure of a patency test or a potential issue with pump function
†after implantation

Highlights

- alfapump reduces LVP requirement in patients with refractory ascities
- alfapump improves 6-month HRQoL compared to SoC in patients with refractory ascities
- sub-study alfapump patients showed nutrition cf. SoC in patients with ascities