Patients with Refractory Ascites Treated with alfapump® System have Better Health-related Quality of Life as Compared to those Treated with Large Volume Paracentesis: The Results of a Multicenter Randomized Controlled Study

Maria Stepanova[1], Fatema Nader[1], Christophe Bureau[2], Danielle Adebayo[3], Laure Elkrief[4], Dominique Valla[4], Markus Peck-Radosavljevic[5], Anne McCune[6], Victor Vargas[7], Macarena Simon-Talero[7], Juan Cordoba[7], Paolo Angeli[8], Silvia Rossi[8], Stewart MacDonald[3], Jeroen Capel[9], Rajiv Jalan[3], Zobair M. Younossi[10]

[1]Center for Outcomes Research in Liver Diseases, Washington DC, USA

[2]Service d'hépato-gastroentérologie, CHU Toulouse, Toulouse, France

[3]UCL Institute of Hepatology, Royal Free Hospital, University College London, London, United Kingdom

[4]DHU UNITY, Service d'hépatologie, Hôpital Beaujon, Clichy, and Université Paris Diderot and Inserm U1149, Paris, France

[5]Department of Gastroenterology/Hepatology, Endocrinology and Nephrology, Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria

[6]Department of Hepatology, Bristol Royal Infirmary, Bristol, United Kingdom

[7]Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d´Hebron, VHIR, Universitat Autònoma de Barcelona, CIBERehd, Barcelona, Spain

[8]Facoltà di Medicina e Chirurgia, Università degli Studi di Padova, Padova, Italy

[9]Sequana Medical AG, Zurich, Switzerland

[10]Department of Medicine, Inova Fairfax Hospital, Falls Church VA, USA

Corresponding author and reprint requests:

Zobair M. Younossi, M.D., M.P.H.

Betty and Guy Beatty Center for Integrated Research

Claude Moore Health Education and Research Building

3300 Gallows Road, Falls Church, VA 22042

Phone: (703) 776-2540 Fax: (703) 776-4386 E-mail: zobair.younossi@inova.org

Word count: 2230

Abstract: 250

Tables and Figures: 3+3

Authors' contributions: MS – data analysis, preparation of the manuscript; FN – project management; CB, DA, LE, DV, MP-R, AM, VV, MS-T, JuC, PA, SR, SM, JeC, RJ – data collection, data interpretation, and manuscript editing; ZMY – study supervision and manuscript revision.

Abbreviations: TIPSS, transjugular intra-hepatic portosystemic shunt; RA, refractory ascites; LVP, large volume paracentesis; HRQL, health-related quality of life; alfapump® system, automated low-flow ascites pump system; BMI, body mass index; SF-36v2, Short Form-36 version 2; CLDQ, Chronic Liver Disease Questionnaire; PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; PCS, physical component summary; MCS, mental component

summary; CLD, chronic liver disease; CPT, Child-Pugh-Turcotte; MELD, Model for End-stage Liver Disease; ALD, alcoholic liver disease; NASH, non-alcoholic steatohepatitis.

ABSTRACT

Background: Refractory ascites (RA) is a complication of cirrhosis which is treated with large-volume paracentesis (LVP) as the standard of care. alfapump® system is a fully implantable pump system which reduces the need for LVP. The aim was to assess health-related quality of life (HRQL) in patients treated with alfapump® vs. LVP. **Methods**: The data was collected in a multicenter open-label randomized controlled trial (clinicaltrials.gov #NCT01528410). Subjects with cirrhosis Child-Pugh class B or C accompanied by RA were randomized to receive alfapump® or LVP. The SF-36v2 and CLDQ scores were compared between the two treatment arms at screening and monthly during treatment. **Results**: Of 60 subjects randomized, HRQL data was available for 58 (N=27 received alfapump® and N=31 received LVP only). At baseline, no differences were seen between the treatment arms (all $p>0.05$): age 61.9±8.4, 79.3% male, MELD scores 11.7±3.3, 85.2% Child-Pugh class B, 70.7% had alcoholic cirrhosis. The mean number of LVP events/subject was lower in alfapump® than LVP (1.1 vs. 8.6, $p<0.001$). The HRQL scores showed a moderate improvement from the baseline levels in subjects treated with alfapump® ($p<0.05$ for Abdominal and Activity scores of CLDQ) but not with LVP (all one-sided $p>0.05$) in the first 3 months. Multivariate analysis showed that treatment with alfapump® was independently associated with better HRQL at 3 months (total CLDQ score: beta=0.67±0.33, $p=0.05$). **Conclusion**: As compared to LVP, the use of alfapump® system is associated with both a reduction in the number of LVP events and improvement of health-related quality of life.

Key words: cirrhosis, decompensation, MELD, alcoholic liver disease

INTRODUCTION

Ascites is pathologic accumulation of peritoneal fluid which is typically associated with a significant volume and hormonal dysregulation in the setting of cirrhosis and portal hypertension [1]. Ascites is a common complication of cirrhosis, with 60% of cirrhotics developing ascites within 10 years of diagnosis [2]. In addition, ascites and other associated complications (spontaneous bacterial peritonitis, hepato-hydrothorax, hepatorenal syndrome and malnutrition) are associated with poor prognosis [1].

The current treatment for ascites consists of different modalities including dietary sodium restriction, pharmacologic therapies, diagnostic and therapeutic paracentesis, and transjugular intra-hepatic portosystemic shunt (TIPSS) [3-4]. Nevertheless, these treatment modalities carry their own risks and complications, with some patients developing diuretic-induced renal dysfunction and hyponatremia as well as diuretic-resistant ascites or refractory ascites (RA). Besides liver transplant, which is the only definitive treatment for RA, large volume paracentesis (LVP) can be used for management of patients with RA [5-6]. Although relatively safe, LVP requires patients to visit the hospital or outpatient clinics as often as weekly. In addition to LVP, TIPSS may be an option for a selected group of patients with RA [7]. Unfortunately, TIPSS placement and subsequent follow-up is contraindicated for some patients with cirrhosis [8-9].

In addition to poor clinical prognosis, many patients with ascites suffer from malnutrition [10-11] and severe impairment of their health-related quality of life (HRQL). Several studies using both generic and disease-specific instruments have indicated that the presence of ascites is associated with severe impairment of HRQL in patients with advanced liver disease [12-16]. In this context,

treatment of RA with alternative strategies may potentially improve patients' HRQL.

One recently developed alternative treatment for RA is the Automated Low-Flow Ascites Pump System (alfapump® system, Sequana Medical AG, Zurich, Switzerland). Alfapump® (alfapump®) system is a fully implantable, programmable, and rechargeable pump system which automatically diverts ascitic fluid from the peritoneal cavity to the urinary bladder, allowing fluid removal by urination [17]. Although preliminary results have been published together with safety and efficacy outcomes, the comprehensive impact of alfapump® system on patients' HRQL has not been reported. Therefore, the purpose of this paper was to compare HRQL of patients who underwent treatment with the alfapump® system to that of patients treated with the standard of care for RA (LVP).

METHODS

Patient population

In this study, we used HRQL data collected in a multicenter randomized controlled study of alfapump® ctpversus LVP in the treatment of RA [17]. The trial was conducted in 6 European centers in 2012-2016 (clinicaltrials.gov #NCT01528410). Adult (18+) patients with cirrhosis confirmed by biopsy and/or clinical and/or radiologic criteria and with RA (that is, "ascites that cannot be mobilized or early recurrence of which after therapeutic paracentesis cannot be satisfactorily prevented by medical therapy" [18]) were randomized 1:1 to either treatment with the alfapump® or evacuation LVP. Excluded were patients with recent gastrointestinal haemorrhage, severe coagulopathy or thrombocytopenia, recurring bacterial peritonitis, evidence of loculated ascites, hepatocellular carcinom that exceeded Milan criteria, HIV infection, body

mass index (BMI) >40, and some other concomitant diseases and conditions [17]. The primary endpoint of the original study was paracentesis-free survival; the HRQL data used in this study was collected as one of secondary endpoints.

Health-related quality of life

Health-related quality of life was assessed at screening and then at 1, 2, 3, and 6 months after the start of treatment using two widely used instruments which were self-administered by patients: Short Form-36 version 2 (SF-36v2) and the Chronic Liver Disease Questionnaire (CLDQ).

The SF-36 instrument includes 36 items grouped into eight non-overlapping domains which represent various aspects of HRQL: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), mental health (MH), all designed to range from 0 to 100. It also includes the physical (PCS) and mental (MCS) component summary scores which are linear combinations of the domains scores adjusted for the inter-domain correlations [19]. The SF-36 instrument can also be used to derive a preference-based health utility score SF-6D which is necessary for quality-adjustment of outcomes in economic analyses. For the purpose of this study, to calculate SF-6D utility scores from SF-36v2, we used a non-parametric Bayesian algorithm as described before [20].

The CLDQ is a disease-specific instrument that was designed and validated to assess HRQL in patients with chronic liver disease (CLD), so that it focuses on the most frequently observed health-related impairments associated with living with CLD. The 29 items are grouped into 6 non-overlapping HRQL domains: Abdominal Symptoms, Activity, Emotional Function, Fatigue,

Systemic Symptoms, and Worry. The total CLDQ score is the average of the six domain scores which all range 1 to 7 [21].

In both instruments, higher scores would indicate a better health status. In order to put the HRQL scores of patients with RA in context, we also collected the population norms from literature for the general population (SF-36 only [22-23]) as well as for patients with non-cirrhotic CLD and with CLD accompanied by compensated (Child-Pugh-Turcotte (CPT) class A) cirrhosis [24-27].

Statistical Analysis

The sample size for this study was driven by the primary endpoint and was not chosen to power our HRQL analysis. Demographics and clinical parameters of the study participants were summarized as N (percentage) or mean ± std.dev in the two treatment arms separately. The HRQL scores changes from patients' own baseline scores were calculated for each HRQL domain and were compared to zero (which would indicate no significant change from baseline) by the sign rank non-parametric test and between the treatment arms using the rank sum test.

Independent association of the changes in the HRQL scores with the RA treatment choice (alfapump® vs. LVP) was assessed in a series of multiple linear regression models. Potential confounders to be adjusted for were as follows: age, gender, BMI, Model for End-stage Liver Disease (MELD) score, CPT class, etiology of CLD (alcoholic liver disease (ALD) vs. other), history of spontaneous bacterial peritonitis, renal failure, hepato-renal syndrome, hepatic encephalopathy, urinary tract infections, and variceal hemorrhage. After a series of bidirectional stepwise selection procedures, only predictors with statistically significant independent association

with the outcome ($p<0.05$) were kept in the models.

All analyses were run in SAS 9.3 (SAS Institute, Cary, NC). The study was separately approved by each site's Institutional Review Board.

RESULTS

Clinical and Demographic Data

A total of 60 patients with refractory ascites were enrolled. Of these subjects, 58 had data to be used for safety and efficacy analysis, including 31 randomized to receive LVP and 27 assigned to the alfapump® system; the remaining 2 patients dropped out before the study (due to obstructive uropathy and to left inguinal hernia). Furthermore, of the intention-to-treat cohort, 10 patients died before the 6 months' time point, 6 received a liver transplant, and 4 subjects discontinued the study in less than 6 months for other reasons. The HRQL data was systematically collected from all available participants for the first 3 months of treatment (N=58 at baseline, 55 at month 1, 51 at month 2, 49 at month 3), and then from a subset of patients at month 6 (N=28). The results of analysis of safety and efficacy endpoints have been published [17]. As reported, the use of alfapump® system led to a substantially longer time to paracentesis (hazard ratio=0.18 (0.09-0.39), $p<0.001$), less paracentesis events (1.1 vs. 8.6 per subject in 6 months after treatment initiation, with 63% of alfapump® patients needing zero paracentesis events, $p<0.001$), and less ascites removed by paracentesis in the alfapump® group. No additional risks for severe adverse events, infection, or mortality was found [17, 28].

Enrolled patients, were, on average, 61.9 ± 8.4 years of age, 79.3% male, 15% had MELD score

of 15 or greater, 85.3% were CPT class B, 70.7% had alcoholic cirrhosis and 12,1% had non-alcoholic steatohepatitis (NASH), 31.0% had history of renal failure, 14.0% had hepatorenal syndrome, 31.6% had hepatic encephalopathy, 24.6% spontaneous bacterial peritonitis, 29.3% variceal hemorrhage, and 60.3% were hospitalized at least once in 3 months prior to enrollment for, on average, a total of 8.5 days. No baseline difference was found between the two treatment arms (**Table 1**).

On-Treatment Health-Related Quality of Life

The baseline HRQL scores of patients with RA are presented in **Table 2**. As shown, all baseline scores were substantially lower in comparison to the general population norms (all $p<0.05$), and nearly all scores were also significantly lower in comparison to patients with CLD without cirrhosis; the only exceptions to the latter were the Mental Health and Emotional Function scores (all $p>0.05$). A number of the HRQL scores were also significantly lower in comparison to compensated cirrhosis patients: $p<0.05$ for PF, RP, GH, VT, SF, and RE of SF-36, as well as for Abdominal Symptoms, Activity and Systemic Symptoms domains of CLDQ (**Table 2**).

One month into treatment, improvements of some aspects of HRQL were noted in patients assigned to alfapump® (**Figure 1**; **Supplementary Table 1** for the specific numbers). In particular, statistically significant improvements were noted in Abdominal Symptoms and Systemic Symptoms scores ($p<0.05$), accompanied by borderline significant improvements in GH and total CLDQ scores ($p<0.10$), and no decrements in other HRQL scores. On the other hand, statistically significant decrements in BP, PCS, and Fatigue scores were experienced by patients receiving LVP ($p\leq0.05$). These trends continued to be observed at the end of the second month.

At 3 months' time point, the trend towards improvement of HRQL scores in the alfapump® arm contrasted to worsening of HRQL in the LVP arm continued, and the magnitudes of improvement became more pronounced (**Figure 2**, **Figure 3**, **Supplementary Table 1**). Furthermore, out of 27 patients who had an improvement in the Abdominal Symptoms score by month 1 and remained in the study till month 3, 81% also had an improvement in that score by month 3, suggesting that HRQL improvement was not only significant but also consistent over time (**Supplementary Table 2**).

In a subgroup analysis of those who also completed 6 months HRQL questionnaires (N=28), a similar pattern was again observed (**Supplementary Table 1**). However, due to smaller sample size reaching this time point, the differences were no longer statistically significant.

Independent predictors of HRQL scores

In multivariate analysis, the use of alfapump® was found to be independently associated with greater HRQL scores, primarily at month 3 of treatment, after adjustment for the baseline levels and other HRQL predictors. The HRQL scores found to be superior in patients using alfapump® included Bodily Pain (SF-36), Vitality (SF-36), Abdominal Symptoms (CLDQ), Activity (CLDQ), Fatigue (CLDQ) and Systemic Symptoms (CLDQ) ($p \leq 0.05$) (**Table 3**). Other predictors of HRQL scores in patients with cirrhosis and RA were age, gender, alcohol-related etiology of liver disease, MELD score, CPT class, and history of complications (hepatorenal syndrome, urinary tract infection, variceal hemorrhage) (**Supplementary Table 3**).

DISCUSSION

This is the first study assessing HRQL of cirrhotic patients with refractory ascites who have undergone treatment with LVP or alfapump® system. Our study confirms severe impairment of HRQL in patients with severe decompensated cirrhosis with refractory ascites. Additionally, our data shows independent predictors of poor HRQL prior to treatment in patients with severe liver disease includes the diagnosis of ALD and male gender. These are consistent with previously reported data [14,27,29-30].

Our results during the treatment period indicate a number of important observations. In particular, subjects with refractory ascites who are treated with LVP continue to worsen their HRQL and experience no HRQL benefit. In contrast, subjects with refractory ascites who were treated with alfapump® system did experience improvement of HRQL as early as 1 month after treatment initiation. In fact, this improvement continued with longer follow-up of those subjects, and clinically meaningful HRQL superiority was noted in multiple domains related to bodily pain, other systemic symptoms, and fatigue [24,31-32]. It is also important to note that the superiority of HRQL in patients treated with alfapump® remained significant even after controlling for other known predictors of HRQL scores. This supports HRQL-related benefits of alfapump® system over LVP. Interestingly, of the two HRQL instruments used, the most consistent improvements were primarily captured by the domains of CLDQ and, in particular, its Abdominal Symptoms domain. This suggests that in patients with advanced liver disease, a disease-specific rather than a generic HRQL instrument is more suitable for capturing changes in HRQL with treatment. This is also consistent with known responsiveness superiority of disease-specific instruments, such as CLDQ [33].

The major limitation for this study is that our sample size was small and became smaller over time as a result of patients dying or receiving liver transplantation. In fact, we were unable to reliably report HRQL at 6 months post-alfapump® insertion because less than half of initially enrolled patients were still available and able to complete the HRQL questionnaires. Despite this, our results suggest that patients with decompensated cirrhosis and RA are still able to experience improvement in their HRQL with successful treatment with alfapump®.

In summary, this preliminary data suggests that receiving alfapump® for treatment of refractory ascites is associated with better HRQL scores that LVP. In this context, we propose that obtaining patients' perspective via assessment of HRQL scores should accompany clinical outcomes and resource utilization metrics in order to assess the full impact of the new treatments. This data, coupled with efficacy, safety, and cost can inform caregivers and policy makers regarding their decisions on how best to best manage important complications of cirrhosis and to provide access to new treatment modalities.

Compliance with Ethical Standards:

Funding: This study was funded by Sequana Medical.

Conflict of interest: ZMY is a consultant or advisory board of Abbvie, Intercept, Gilead Sciences, Salix, GSK, BMS, Allergan, Sanofi and NovoNordik. RJ has research collaborations with Ocera, and Yaqrit, consults for Ocera and Yaqrit and has received speaking and consultation fees from Sequana. RJ is the founder of Yaqrit Limited, which is developing UCL inventions for treatment of patients with cirrhosis. LE had received funding from Sequana for reporting of the data into the

CRF for this study. DV 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 Sciences. PA is a member of the Sequana Medical AG Advisory Board, the LAT Pharma LLC Advisory Board, and the Gilead Advisory Board in Italy. Other coauthors have indicated they have no potential conflicts of interest to disclose.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

REFERENCES

1. Moore CM, Van Thiel DH. Cirrhotic ascites review: Pathophysiology, diagnosis and management. World J Hepatol. 2013 May 27; 5(5): 251–263.
2. Planas R, Montoliu S, Ballesté B, Rivera M, Miquel M, Masnou H, et al. Natural history of patients hospitalized for management of cirrhotic ascites. Clin Gastroenterol Hepatol. 2006 Nov;4(11):1385-94.
3. Runyon BA, AASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: an update. Hepatology. 2009 Jun;49(6):2087-107.
4. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol. 2010 Sep;53(3):397-417.
5. Barsuk JH, Cohen ER, Feinglass J, McGaghie WC, Wayne DB. Clinical outcomes after

bedside and interventional radiology paracentesis procedures. Am J Med. 2013 Apr;126(4):349-56.

6. Barsuk JH, Feinglass J, Kozmic SE, Hohmann SF, Ganger D, Wayne DB. Specialties performing paracentesis procedures at university hospitals: implications for training and certification. J Hosp Med. 2014 Mar;9(3):162-8. doi: 10.1002/jhm.2153. Epub 2014 Feb 3.
7. Smith M, Durham J. Evolving Indications for TIPS. Tech Vasc Interv Radiol. 2016 Mar;19(1):36-41.
8. Copelan A, Kapoor B, Sands M. Transjugular intrahepatic portosystemic shunt: indications, contraindications, and patient work-up. Semin Intervent Radiol. 2014 Sep;31(3):235-42.
9. American College of Radiology, Society for Pediatric Radiology, and Society for Interventional Radiology, ACR-SIR-SPR practice parameter for the creation of a transjugular intrahepatic portosystemic shunt (TIPS), Amended 2014 (Resolution 39). Practice Parameters and Technical Standards, 2014: p. 1-22.
10. Teiusanu A, Andrei M, Arbanas T, Nicolaie T, Diculescu M. Nutritional status in cirrhotic patients. Maedica (Buchar). 2012 Dec;7(4):284-9.
11. Sorrentino P, Castaldo G, Tarantino L, Bracigliano A, Perrella A, Perrella O, et al. Preservation of nutritional-status in patients with refractory ascites due to hepatic cirrhosis who are undergoing repeated paracentesis. J Gastroenterol Hepatol. 2012 Apr;27(4):813-22.
12. Younossi ZM, Boparai N, McCormick M, Price LL, Guyatt G. Assessment of utilities and health-related quality of life in patients with chronic liver disease. Am J

Gastroenterol. 2001 Feb;96(2):579-83.

13. Solà E, Watson H, Graupera I, Turón F, Barreto R, Rodríguez E, et al. Factors related to quality of life in patients with cirrhosis and ascites: relevance of serum sodium concentration and leg edema. J Hepatol. 2012 Dec;57(6):1199-206.
14. Orr JG, Homer T, Ternent L, Newton J, McNeil CJ, Hudson M, et al. Health related quality of life in people with advanced chronic liver disease. J Hepatol. 2014 Nov;61(5):1158-65.
15. Bhanji RA, Carey EJ, Watt KD. Review article: maximising quality of life while aspiring for quantity of life in end-stage liver disease. Aliment Pharmacol Ther. 2017 Jul;46(1):16-25.
16. Jara M, Bednarsch J, Malinowski M, Lüttgert K, Orr J, Puhl G, Seehofer D, Neuhaus P, Stockmann M. Predictors of quality of life in patients evaluated for liver transplantation. Clin Transplant. 2014 Dec;28(12):1331-8.
17. Bureau C, Adebayo D, Chalret de Rieu M, Elkrief L, Valla D, Peck-Radosavljevic M, et al. Alfapump® system vs. large volume paracentesis for refractory ascites: A multicenter randomized controlled study. J Hepatol. 2017 Jun 21. doi: 10.1016/j.jhep.2017.06.010. [Epub ahead of print]
18. Moore KP, Aithal GP. Guidelines on the management of ascites in cirrhosis. Gut. 2006 Oct;55 Suppl 6:vi1-12.
19. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun; 30(6):473-83.
20. Kharroubi SA, Brazier JE, Roberts J, O'Hagan A. Modelling SF-6D health state preference data using a nonparametric Bayesian method. J Health Econ. 2007 May 1;

26(3):597-612.

21. Younossi ZM, Stepanova M, Henry L. Performance and Validation of Chronic Liver Disease Questionnaire-Hepatitis C Version (CLDQ-HCV) in Clinical Trials of Patients with Chronic Hepatitis C. Value Health. 2016; 19(5):544-51.
22. Ware JE, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. User's manual for the SF-36v2 Health Survey. 2nd ed. QualityMetric Incorporated; Lincoln, RI: 2007.
23. Fryback DG, Dunham NC, Palta M, Hanmer J, Buechner J, Cherepanov D, et al. US norms for six generic health-related quality-of-life indexes from the National Health Measurement study. Med Care. 2007 Dec;45(12):1162-70.
24. Younossi ZM, Guyatt G, Kiwi M, Boparai N, King D. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. Gut. 1999 Aug;45(2):295-300.
25. Sayiner M, Stepanova M, Pham H, Noor B, Walters M, Younossi ZM. Assessment of health utilities and quality of life in patients with non-alcoholic fatty liver disease. BMJ Open Gastroenterol. 2016 Aug 16;3(1):e000106.
26. Campbell MS, Brensinger CM, Sanyal AJ, Gennings C, Wong F, Kowdley KV, et al. Quality of life in refractory ascites: transjugular intrahepatic portal-systemic shunting versus medical therapy. Hepatology. 2005 Sep;42(3):635-40.
27. Afendy A, Kallman JB, Stepanova M, Younoszai Z, Aquino RD, Bianchi G, Marchesini G, Younossi ZM. Predictors of health-related quality of life in patients with chronic liver disease. Aliment Pharmacol Ther. 2009 Sep 1;30(5):469-76.
28. Adebayo D, Bureau C, Valla D, Peck-Radosavljevic M, McCune A, Vargas V, et al.

Alfapump® system versus large volume paracentesis in the treatment of refractory ascites. A multicenter randomised controlled study. J Hepatol. 2015 April;62 Suppl 2:S849–S850.

29. Paparrigopoulos T, Tzavellas E, Karaiskos D, Liappas I. Hepatology. Should impaired liver function be held responsible for cognitive impairment and poor health-related quality of life in alcoholic cirrhosis? 2007 Sep;46(3):950; author reply 951.
30. Imtiaz S, Loheswaran G, Le Foll B, Rehm J. Longitudinal alcohol consumption patterns and health-related quality of life: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug Alcohol Rev. 2017 Mar 14. doi: 10.1111/dar.12503. [Epub ahead of print]
31. Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. Hepatology. 2005 Apr;41(4):790-800.
32. Walters SJ, Brazier JE. What is the relationship between the minimally important difference and health state utility values? The case of the SF-6D. Health Qual Life Outcomes. 2003 Apr 11;1:4.
33. Loria A, Escheik C, Gerber NL, Younossi ZM. Quality of life in cirrhosis. Curr Gastroenterol Rep. 2013 Jan;15(1):301. doi: 10.1007/s11894-012-0301-5. Review. PubMed PMID: 23250701.

Table 1. Demographics and medical history of the study participants by the treatment arm.

	alfapump®	LVP	p
N	27	31	
Age, years	61.1 ± 8.5	62.6 ± 8.4	0.54
BMI, kg/m^2	27.7 ± 4.8	27.3 ± 5.7	0.60
Male gender	21 (77.8%)	25 (80.6%)	0.79
MELD score	12.2 ± 2.5	11.3 ± 3.9	0.08
MELD score ≥ 15	4 (15.4%)	4 (13.8%)	0.87
CPT class B	22 (88.0%)	24 (82.8%)	0.59
CPT class C	3 (12.0%)	5 (17.2%)	0.59
Etiology of CLD:			
ALD	20 (74.1%)	21 (67.7%)	0.10
NASH	5 (18.5%)	2 (6.5%)	
Other	2 (7.4%)	8 (25.8%)	
History of:			
Renal failure	11 (40.7%)	7 (22.6%)	0.14
Hepatorenal syndrome	4 (14.8%)	4 (13.3%)	0.87
Hepatic encephalopathy	8 (29.6%)	10 (33.3%)	0.76
Spontaneous bacterial peritonitis	7 (26.9%)	7 (22.6%)	0.70
Urinary tract infection	1 (3.8%)	3 (9.7%)	0.39
Variceal hemorrhage	11 (40.7%)	6 (19.4%)	0.07
Hospitalized in previous 3 months	14 (51.9%)	21 (67.7%)	0.22
Hospitalization duration, days	7.5 ± 6.1	9.2 ± 6.8	0.26

Table 2. Baseline HRQL scores by the SF-36 instrument (mean ± std.dev.) in patients with RA.

HRQL domain (†norms)	alfapump® (N=27)	LVP (N=31)	P	All RA patients (N=58)	General population [22,23]	Non-cirrhotic CLD [24-25]	CLD with compensated cirrhosis [24-25]	RA, 12 months of TIPS [26]
SF-36 (range 0-100)								
Physical Functioning	40.77 ± 24.20	40.35 ± 27.36	0.97	40.55 ± 25.71	80.30 [a]	79.57 [b]	57.95 [c]	NA
Role Physical	28.01 ± 25.26	32.66 ± 26.75	0.49	30.50 ± 25.94	80.08 [a]	65.79 [b]	43.42 [c]	NA
Bodily Pain	49.15 ± 21.37	56.97 ± 33.98	0.41	53.33 ± 28.84	70.24 [a]	72.51 [b]	57.59	NA
General Health	38.18 ± 13.18	36.23 ± 22.44	0.41	37.14 ± 18.58	65.30 [a]	63.65 [b]	45.42 [c]	NA
Vitality	38.66 ± 17.42	41.60 ± 26.88	0.93	40.23 ± 22.82	57.03 [a]	49.91 [b]	45.51 [c]	NA
Social Functioning	56.02 ± 24.36	52.02 ± 30.63	0.57	53.88 ± 27.72	81.70 [a]	76.60 [b]	67.95 [c]	NA
Role Emotional	47.22 ± 32.03	52.69 ± 32.30	0.50	50.14 ± 32.01	85.24 [a]	73.68 [b]	65.77 [c]	NA
Mental Health	67.04 ± 21.3	63.55 ± 21.76	0.54	65.17 ± 21.44	73.34 [a]	48.10	60.21	NA
Physical Component Summary	34.70 ± 7.67	36.01 ± 10.09	0.46	35.40 ± 8.99	50.00 [a]	49.82 [b]	36.96	33.4
Mental Component Summary	43.50 ± 9.76	43.04 ± 12.46	0.76	43.25 ± 11.19	50.00 [a]	40.99	45.80	48.0 [d]
SF-6D health utility (range 0-1)	0.57 ± 0.07	0.56 ± 0.14	0.82	0.56 ± 0.11	0.79 [a]	0.66 [b]	0.55	NA
CLDQ (range 1-7)								
Abdominal symptoms	3.90 ± 1.12	3.96 ± 1.85	0.79	3.93 ± 1.54	N/A	5.50 [b]	4.88 [c]	NA
Activity	3.76 ± 1.20	4.18 ± 1.78	0.40	3.99 ± 1.54	N/A	5.64 [b]	4.57 [c]	NA
Emotional function	4.76 ± 1.18	4.45 ± 1.37	0.31	4.59 ± 1.28	N/A	4.67	4.50	NA
Fatigue	3.68 ± 1.16	3.96 ± 1.54	0.63	3.83 ± 1.37	N/A	4.48 [b]	3.57	NA
Systemic symptoms	4.19 ± 0.97	4.50 ± 1.47	0.43	4.36 ± 1.26	N/A	5.36 [b]	4.74 [c]	NA
Worry	4.41 ± 1.66	4.05 ± 1.91	0.54	4.22 ± 1.79	N/A	5.19 [b]	4.57	NA
Total	4.12 ± 0.96	4.18 ± 1.41	0.96	4.15 ± 1.21	N/A	5.14 [b]	4.47	NA

Note: the RA cohort score is significantly lower ($p<0.05$) than the score from: [a] general population; [b] non-cirrhotic CLD; [c] CLD with compensated cirrhosis; [d] RA patients after 12 months of TIPS (PCS and MCS only); N/A – not applicable; NA – not available.

Table 3. Independent association of the RA treatment choice with treatment-emergent changes in HRQL scores ($p \leq 0.05$ only). * Beta indicates the magnitude of superiority in HRQL scores in those receiving alfapump® with reference to those receiving LVP given that all other HRQL predictors (baseline HRQL score, age, gender, CPT class, MELD score, CLD etiology, comorbid conditions) are held equal.

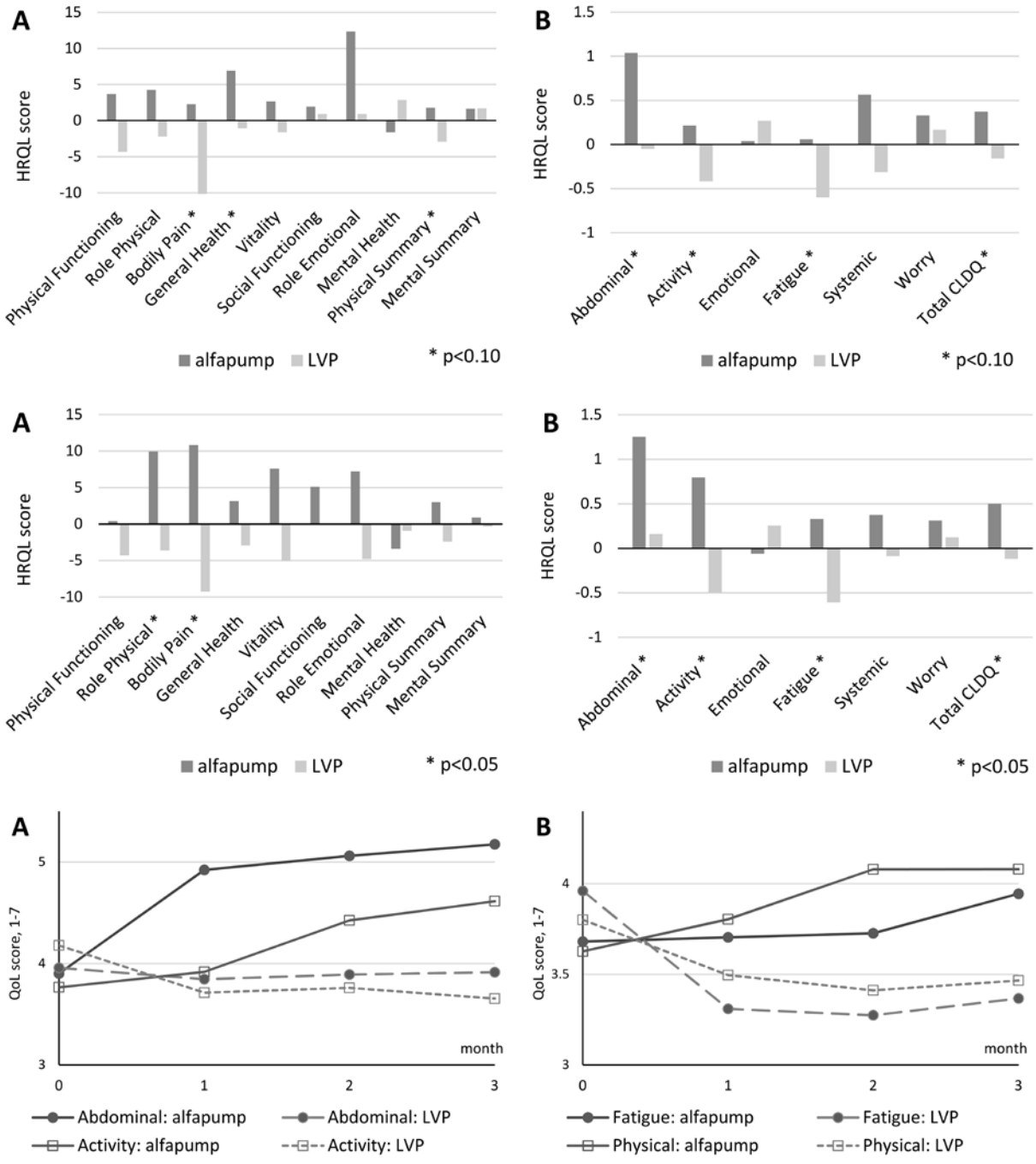
HRQL score at time point	Range for the score	Beta *	Std.err.	p
Sf-36 Bodily Pain at month 3	0-100	23.92	8.07	0.0048
SF-36 Vitality at month 3	0-100	12.24	6.29	0.0500
SF-36 Physical Summary month 1	25-60	4.73	1.91	0.0168
CLDQ-Abdominal Symptoms at month 1	1-7	1.09	0.47	0.0248
CLDQ-Abdominal Symptoms at month 3	1-7	0.92	0.44	0.0403
CLDQ-Activity at month 3	1-7	1.26	0.33	0.0005
CLDQ-Activity at month 6	1-7	1.01	0.38	0.0136
CLDQ-Fatigue at month 3	1-7	0.92	0.37	0.0171
CLDQ-Systemic Symptoms at month 1	1-7	0.88	0.28	0.0027
Total CLDQ score at month 1	1-7	0.53	0.23	0.0268

FIGURE LEGENDS

Figure 1. Mean changes in HRQL scores measured by (A) SF-36 and (B) CLDQ in patients with RA from baseline to treatment month 1 by the treatment arm.

Figure 2. Mean changes in HRQL scores measured by (A) SF-36 and (B) CLDQ in patients with RA from baseline to treatment month 3 by the treatment arm.

Figure 3. Mean HRQL scores in patients with RA from baseline to treatment month 3. Physical score (PCS of SF-36) was transformed from its original scale to a 1-7 scale for presentation purpose.



Supplementary Table 1. Treatment-emergent changes in the HRQL scores in patients with RA

by the treatment arm (mean ± std.err.); a positive change indicates improvement of the HRQL score. The minimal clinically important difference (MCID) for SF-36 is 4.2 points [31], for SF-6D is 3.3 [32], for CLDQ is 0.5 points [24].

Time point / HRQL	alfapump®	$p^{\ddagger}$	LVP	$p^{\ddagger}$	$p^{\dagger}$
Month 1					
Physical Functioning	3.67 ± 4.63	0.48	-4.33 ± 5.61	0.72	0.56
Role Physical	4.25 ± 3.76	0.25	-2.23 ± 3.27	0.59	0.26
Bodily Pain	2.27 ± 5.92	0.46	-11.00 ± 5.45	0.0577	0.0672
General Health	6.90 ± 3.51	0.0739	-1.07 ± 2.61	0.70	0.0794
Vitality	2.64 ± 3.75	0.55	-1.64 ± 3.03	0.52	0.34
Social Functioning	1.92 ± 4.99	0.60	0.89 ± 4.59	0.95	0.77
Role Emotional	12.33 ± 8.59	0.19	0.89 ± 5.36	0.87	0.46
Mental Health	-1.63 ± 3.07	0.39	2.86 ± 3.38	0.27	0.12
Physical Summary	1.78 ± 1.43	0.19	-2.95 ± 1.28	0.0510	0.0284
Mental Summary	1.63 ± 1.89	0.39	1.72 ± 1.83	0.46	0.93
SF-6D utility	1.09 ± 1.84	0.42	-2.34 ± 1.91	0.22	0.13
Abdominal Symptoms	1.04 ± 0.36	0.0078	-0.05 ± 0.31	0.95	0.0306
Activity	0.21 ± 0.28	0.38	-0.42 ± 0.24	0.10	0.0746
Emotional Function	0.04 ± 0.20	0.54	0.27 ± 0.24	0.48	0.83
Fatigue	0.06 ± 0.25	0.92	-0.60 ± 0.16	0.0010	0.0501
Systemic Symptoms	0.56 ± 0.17	0.0014	-0.31 ± 0.21	0.15	0.0030
Worry	0.33 ± 0.23	0.19	0.16 ± 0.18	0.56	0.52
Total CLDQ	0.37 ± 0.19	0.0532	-0.16 ± 0.14	0.24	0.0323
Month 2					
Physical Functioning	3.14 ± 6.50	0.55	-11.07 ± 5.66	0.0901	0.13
Role Physical	1.99 ± 4.34	0.43	-4.31 ± 3.59	0.31	0.22
Bodily Pain	3.23 ± 6.26	0.33	-6.90 ± 5.46	0.40	0.0623
General Health	9.34 ± 4.97	0.0782	-0.66 ± 2.57	0.80	0.13
Vitality	0.00 ± 3.99	0.89	-5.68 ± 3.24	0.10	0.23
Social Functioning	-6.25 ± 6.41	0.35	-4.74 ± 3.84	0.17	0.88
Role Emotional	-1.32 ± 8.54	0.86	-4.02 ± 4.82	0.65	0.91
Mental Health	-6.36 ± 3.55	0.15	0.00 ± 3.43	0.81	0.27
Physical Summary	3.14 ± 1.53	0.0600	-3.04 ± 1.60	0.14	0.0117
Mental Summary	-3.09 ± 2.01	0.15	-0.43 ± 1.81	0.87	0.31
SF-6D utility	-1.44 ± 1.84	0.49	-2.97 ± 2.54	0.33	0.70
Abdominal Symptoms	1.18 ± 0.39	0.0061	0.10 ± 0.31	0.78	0.0427
Activity	0.56 ± 0.29	0.0704	-0.35 ± 0.21	0.12	0.0168
Emotional Function	-0.11 ± 0.21	0.96	0.08 ± 0.26	0.73	0.72
Fatigue	0.04 ± 0.31	0.90	-0.62 ± 0.17	0.0009	0.0798
Systemic Symptoms	0.15 ± 0.23	0.38	-0.19 ± 0.19	0.58	0.34
Worry	0.23 ± 0.24	0.30	-0.04 ± 0.31	0.87	0.63
Total CLDQ	0.34 ± 0.19	0.0820	-0.17 ± 0.17	0.51	0.0479
Month 3					
Physical Functioning	0.41 ± 4.71	0.72	-4.29 ± 6.17	0.56	0.62
Role Physical	9.94 ± 5.90	0.14	-3.63 ± 3.76	0.30	0.0464
Bodily Pain	10.82 ± 5.48	0.11	-9.26 ± 6.42	0.21	0.0406
General Health	3.14 ± 4.61	0.56	-2.95 ± 3.33	0.52	0.53
Vitality	7.58 ± 4.86	0.15	-5.09 ± 4.54	0.30	0.0607

Social Functioning	5.11 ± 5.50	0.40	0.00 ± 5.12	0.89	0.41
Role Emotional	7.20 ± 9.58	0.51	-4.81 ± 6.14	0.47	0.34
Mental Health	-3.41 ± 4.87	0.29	-0.93 ± 4.24	0.84	0.57
Physical Summary	2.98 ± 1.69	0.14	-2.44 ± 1.88	0.30	0.0769
Mental Summary	0.91 ± 2.54	0.63	-0.35 ± 2.43	0.90	0.63
SF-6D utility	1.79 ± 1.85	0.41	-1.82 ± 2.82	0.41	0.27
Abdominal Symptoms	1.25 ± 0.27	0.0002	0.16 ± 0.32	0.62	0.0158
Activity	0.80 ± 0.23	0.0012	-0.50 ± 0.27	0.13	0.0011
Emotional Function	-0.06 ± 0.24	0.81	0.25 ± 0.32	0.62	0.71
Fatigue	0.33 ± 0.29	0.39	-0.61 ± 0.25	0.0127	0.0100
Systemic Symptoms	0.37 ± 0.22	0.0991	-0.09 ± 0.23	0.96	0.17
Worry	0.31 ± 0.30	0.30	0.12 ± 0.31	0.78	0.53
Total CLDQ	0.50 ± 0.20	0.0201	-0.12 ± 0.21	0.57	0.0489
Month 6 *					
Physical Functioning	-1.92 ± 8.89	0.52	-5.60 ± 5.41	0.38	0.79
Role Physical	8.33 ± 5.72	0.18	-10.55 ± 5.03	0.0525	0.0152
Bodily Pain	-6.25 ± 9.09	0.85	-4.75 ± 7.08	0.49	0.93
General Health	3.77 ± 5.08	0.65	-8.81 ± 4.88	0.0366	0.12
Vitality	-2.08 ± 4.42	0.59	-13.80 ± 7.12	0.0658	0.16
Social Functioning	-4.81 ± 9.76	0.79	-10.16 ± 7.15	0.16	0.41
Role Emotional	9.09 ± 13.46	0.72	-12.50 ± 7.49	0.12	0.22
Mental Health	-8.85 ± 7.45	0.0850	-5.31 ± 5.78	0.41	0.43
Physical Summary	0.76 ± 2.47	0.85	-2.43 ± 2.04	0.35	0.29
Mental Summary	-2.53 ± 3.25	0.38	-5.04 ± 3.03	0.19	0.64
SF-6D utility	-2.75 ± 4.55	0.70	-0.06 ± 3.16	0.84	0.76
Abdominal Symptoms	0.18 ± 0.46	0.68	-0.33 ± 0.46	0.67	0.68
Activity	0.21 ± 0.25	0.54	-0.83 ± 0.30	0.0181	0.0094
Emotional Function	-0.77 ± 0.41	0.0708	0.06 ± 0.37	0.84	0.13
Fatigue	-0.23 ± 0.27	0.35	-0.67 ± 0.35	0.0458	0.23
Systemic Symptoms	-0.12 ± 0.30	0.80	-0.02 ± 0.34	0.87	1.00
Worry	0.07 ± 0.41	1.00	0.18 ± 0.51	0.61	0.58
Total CLDQ	-0.11 ± 0.27	0.89	-0.27 ± 0.30	0.45	0.70

$p^{\ddagger}$ comparison of the change to zero ($p>0.05$ indicates no significant change)
$p^{\dagger}$ comparison of the changes between the study arms
* the 6 months' time point was calculated in a subset of subjects only (N=28)

References from the manuscript:

24. Younossi ZM, Guyatt G, Kiwi M, Boparai N, King D. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. Gut. 1999 Aug;45(2):295-300.
31. Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. Hepatology. 2005 Apr;41(4):790-800.
32. Walters SJ, Brazier JE. What is the relationship between the minimally important difference and health state utility values? The case of the SF-6D. Health Qual Life Outcomes. 2003 Apr 11;1:4.

Supplementary Table 2. Comparison of patients who improved and did not improve their

Abdominal Symptoms score by month 1. p‡ comparison of the change to zero (p>0.05 indicates no significant change); p† comparison of the changes between the study arms.

	Improved by month 1	p‡	Not improved by month 1	p‡	p†
N	29		26		
Treated with alfapump®	18 (62.1%)		8 (30.8%)		0.0203
Age, years	61.552 ± 8.420		62.308 ± 8.835		0.97
BMI, kg/m^2	27.077 ± 5.348		27.913 ± 4.812		0.51
Male gender	22 (75.9%)		21 (80.8%)		0.66
MELD score	11.931 ± 3.184		11.739 ± 3.633		0.69
MELD score ≥ 15	4 (13.8%)		4 (17.4%)		0.72
CPT class B	22 (78.6%)		21 (91.3%)		0.21
CPT class C	6 (21.4%)		2 (8.7%)		0.21
Etiology: ALD	19 (65.5%)		20 (76.9%)		0.35
Etiology: NASH	6 (20.7%)		1 (3.8%)		0.0613
Etiology: other	4 (13.8%)		5 (19.2%)		0.29
Renal failure	9 (31.0%)		8 (30.8%)		0.98
Hepatorenal syndrome	4 (13.8%)		4 (16.0%)		0.82
Hepatic encephalopathy	10 (34.5%)		8 (32.0%)		0.85
Spontaneous bacterial peritonitis	8 (28.6%)		5 (19.2%)		0.42
Urinary tract infection	3 (10.7%)		1 (3.8%)		0.34
Variceal hemorrhage	11 (37.9%)		5 (19.2%)		0.13
Hospitalized in previous 3 months	16 (55.2%)		16 (61.5%)		0.63
Hospitalization duration, days	8.000 ± 5.574		10.000 ± 7.581		0.44
Baseline HRQL scores					
SF-36					
Physical Functioning	35.594 ± 21.961		46.139 ± 27.167		0.11
Role Physical	28.664 ± 24.293		32.452 ± 28.396		0.68
Bodily Pain	44.655 ± 22.041		63.308 ± 30.989		0.0199
General Health	36.966 ± 14.512		38.346 ± 23.020		0.97
Vitality	35.991 ± 21.628		44.792 ± 24.262		0.22
Social Functioning	51.724 ± 26.247		55.769 ± 27.439		0.59
Role Emotional	46.839 ± 27.586		51.923 ± 36.917		0.58
Mental Health	61.379 ± 21.418		68.654 ± 21.705		0.21
Physical Component Summary	33.884 ± 7.180		37.485 ± 10.239		0.17
Mental Component Summary	41.840 ± 10.462		44.193 ± 12.025		0.40
SF-6D health utility	54.041 ± 9.310		59.534 ± 11.659		0.0448
CLDQ					
Abdominal Symptoms	3.241 ± 1.130		4.615 ± 1.580		0.0002
Activity	3.695 ± 1.175		4.192 ± 1.843		0.36
Emotional Function	4.230 ± 1.205		4.938 ± 1.253		0.0277
Fatigue	3.462 ± 1.207		4.146 ± 1.466		0.0542
Systemic Symptoms	3.855 ± 1.015		4.835 ± 1.307		0.0069
Worry	3.800 ± 1.627		4.631 ± 1.869		0.0696
Total CLDQ	3.714 ± 0.959		4.560 ± 1.272		0.0042

Treatment-emergent changes by month 1 (N=55)

Physical Functioning	3.895 ± 4.498	0.46	-5.190 ± 5.848	0.70	0.46
Role Physical	1.563 ± 3.879	0.57	0.000 ± 3.083	0.76	0.51
Bodily Pain	7.929 ± 4.850	0.11	-18.115 ± 5.643	0.0008	0.0028
General Health	6.304 ± 3.181	0.0599	-1.038 ± 2.950	0.73	0.0824
Vitality	3.125 ± 3.440	0.43	-2.484 ± 3.271	0.45	0.28
Social Functioning	5.804 ± 4.832	0.24	-3.365 ± 4.523	0.46	0.15
Role Emotional	12.500 ± 6.971	0.0877	-0.666 ± 6.921	0.70	0.17
Mental Health	0.893 ± 3.264	0.67	0.481 ± 3.276	0.89	0.63
Physical Component Summary	1.511 ± 1.175	0.31	-3.214 ± 1.538	0.0639	0.0589
Mental Component Summary	2.698 ± 1.744	0.0833	0.540 ± 1.971	0.87	0.17
SF-6D health utility	2.852 ± 1.417	0.0967	-4.737 ± 2.096	0.0359	0.0027
Abdominal Symptoms	1.833 ± 0.219	<0.0001	-1.064 ± 0.192	<0.0001	<0.0001
Activity	0.322 ± 0.222	0.15	-0.615 ± 0.276	0.0351	0.0150
Emotional Function	0.491 ± 0.242	0.0237	-0.212 ± 0.169	0.17	0.0134
Fatigue	0.055 ± 0.221	0.94	-0.673 ± 0.179	0.0007	0.0105
Systemic Symptoms	0.652 ± 0.174	0.0009	-0.515 ± 0.189	0.0132	0.0001
Worry	0.667 ± 0.216	0.0038	-0.235 ± 0.143	0.0916	0.0030
Total CLDQ	0.670 ± 0.140	<0.0001	-0.552 ± 0.105	<0.0001	<0.0001
Treatment-emergent changes by month 2 (N=49)					
Physical Functioning	2.139 ± 5.578	0.78	-10.664 ± 6.444	0.21	0.26
Role Physical	-2.083 ± 4.647	0.81	-1.420 ± 3.048	0.79	0.99
Bodily Pain	7.667 ± 4.704	0.10	-16.818 ± 6.570	0.0468	0.0176
General Health	8.444 ± 3.905	0.0744	-2.114 ± 3.563	0.62	0.12
Vitality	-0.231 ± 3.522	0.85	-7.197 ± 3.289	0.0499	0.16
Social Functioning	-3.704 ± 4.103	0.24	-6.250 ± 6.030	0.40	0.74
Role Emotional	-2.469 ± 7.481	0.75	-3.787 ± 5.135	0.79	0.97
Mental Health	-2.778 ± 3.162	0.45	-2.045 ± 3.874	0.89	0.54
Physical Component Summary	2.594 ± 1.533	0.15	-3.854 ± 1.784	0.14	0.0466
Mental Component Summary	-2.039 ± 1.752	0.35	-1.008 ± 2.077	0.58	0.86
SF-6D health utility	0.108 ± 1.814	0.95	-5.526 ± 2.753	0.0799	0.15
Abdominal Symptoms	1.500 ± 0.276	<0.0001	-0.606 ± 0.314	0.0774	0.0001
Activity	0.253 ± 0.252	0.62	-0.273 ± 0.281	0.41	0.33
Emotional Function	0.026 ± 0.257	0.53	-0.094 ± 0.229	0.73	0.51
Fatigue	-0.222 ± 0.267	0.40	-0.511 ± 0.214	0.0335	0.53
Systemic Symptoms	0.230 ± 0.194	0.16	-0.377 ± 0.231	0.16	0.0361
Worry	0.350 ± 0.268	0.17	-0.191 ± 0.328	0.84	0.17
Total CLDQ	0.356 ± 0.177	0.0216	-0.342 ± 0.173	0.0820	0.0055
Treatment-emergent changes by month 3 (N=47)					
Physical Functioning	2.140 ± 4.979	0.69	-7.730 ± 7.013	0.36	0.38
Role Physical	2.315 ± 4.576	0.66	2.917 ± 5.895	0.87	0.57
Bodily Pain	3.370 ± 6.387	0.60	-6.250 ± 6.831	0.38	0.52
General Health	1.000 ± 3.491	0.92	-1.638 ± 4.889	0.84	0.86
Vitality	4.012 ± 5.161	0.38	-4.896 ± 4.159	0.32	0.21
Social Functioning	5.556 ± 5.515	0.34	-1.250 ± 5.122	0.78	0.36
Role Emotional	0.617 ± 7.678	0.88	-0.877 ± 8.805	0.60	0.99
Mental Health	-2.593 ± 4.033	0.55	-1.500 ± 5.478	0.59	0.85
Physical Component Summary	1.478 ± 1.966	0.35	-1.915 ± 1.848	0.33	0.20
Mental Component Summary	0.071 ± 2.282	0.86	0.097 ± 2.927	0.96	0.91
SF-6D health utility	1.129 ± 1.638	0.70	-3.544 ± 3.958	0.38	0.28

Abdominal Symptoms	1.370 ± 0.210	<0.0001	-0.458 ± 0.343	0.28	0.0001
Activity	0.457 ± 0.229	0.0237	-0.450 ± 0.354	0.21	0.0257
Emotional Function	0.420 ± 0.238	0.0926	-0.325 ± 0.340	0.23	0.0224
Fatigue	0.222 ± 0.262	0.61	-0.785 ± 0.295	0.0059	0.0104
Systemic Symptoms	0.600 ± 0.180	0.0034	-0.530 ± 0.263	0.0676	0.0011
Worry	0.533 ± 0.224	0.0277	-0.103 ± 0.410	0.64	0.11
Total CLDQ	0.600 ± 0.148	0.0003	-0.450 ± 0.255	0.0532	0.0008
Treatment-emergent changes by month 6 (N=27)					
Physical Functioning	-3.073 ± 7.978	0.55	-5.220 ± 4.373	0.31	0.78
Role Physical	0.000 ± 4.883	0.91	-7.500 ± 8.112	0.38	0.19
Bodily Pain	-1.176 ± 6.989	0.91	-15.300 ± 9.220	0.14	0.26
General Health	-0.824 ± 4.578	0.97	-6.818 ± 6.694	0.17	0.20
Vitality	-6.372 ± 6.282	0.23	-12.121 ± 6.909	0.0859	0.62
Social Functioning	-5.147 ± 8.025	0.59	-13.636 ± 8.991	0.17	0.49
Role Emotional	-2.084 ± 9.208	0.59	-8.332 ± 13.088	0.58	0.63
Mental Health	-8.529 ± 5.716	0.15	-4.545 ± 8.406	0.44	0.91
Physical Component Summary	0.557 ± 2.299	0.75	-4.088 ± 1.820	0.0645	0.13
Mental Component Summary	-4.037 ± 2.630	0.12	-4.415 ± 4.379	0.43	0.84
SF-6D health utility	-0.180 ± 3.636	0.90	-3.340 ± 4.219	0.64	0.49
Abdominal Symptoms	0.020 ± 0.403	1.00	-0.467 ± 0.580	0.46	0.50
Activity	-0.186 ± 0.266	0.39	-0.667 ± 0.419	0.18	0.20
Emotional Function	-0.261 ± 0.461	0.97	-0.393 ± 0.153	0.0527	0.27
Fatigue	-0.353 ± 0.328	0.30	-0.640 ± 0.302	0.0566	0.38
Systemic Symptoms	0.282 ± 0.323	0.35	-0.625 ± 0.229	0.0234	0.11
Worry	0.291 ± 0.496	0.37	-0.030 ± 0.368	0.98	0.48
Total CLDQ	-0.034 ± 0.301	0.71	-0.470 ± 0.205	0.0410	0.11
Treatment-emergent changes by month 9 (N=17)					
Abdominal Symptoms	0.611 ± 0.506	0.38	0.200 ± 0.403	1.00	0.75
Activity	0.222 ± 0.399	0.65	0.667 ± 0.279	0.13	0.96
Emotional Function	0.167 ± 0.518	0.35	-0.304 ± 0.203	0.25	0.17
Fatigue	0.217 ± 0.333	0.29	-0.280 ± 0.492	0.63	0.43
Systemic Symptoms	0.817 ± 0.346	0.0371	-0.760 ± 0.440	0.31	0.0448
Worry	0.279 ± 0.488	0.56	0.560 ± 0.578	0.38	0.96
Total CLDQ	0.385 ± 0.331	0.0923	0.014 ± 0.309	1.00	0.25
Treatment-emergent changes by month 12 (N=13)					
Abdominal Symptoms	1.222 ± 0.567	0.0781	-1.000 ± 1.036	0.50	0.0879
Activity	-0.037 ± 0.517	0.93	0.333 ± 0.236	0.38	0.49
Emotional Function	-0.069 ± 0.438	0.48	-0.281 ± 0.299	0.75	1.00
Fatigue	0.133 ± 0.189	0.38	-0.650 ± 0.780	0.63	0.39
Systemic Symptoms	0.400 ± 0.328	0.30	-0.350 ± 0.263	0.50	0.18
Worry	1.000 ± 0.431	0.0391	0.700 ± 0.238	0.13	0.44
Total CLDQ	0.442 ± 0.096	0.0039	-0.208 ± 0.335	1.00	0.0449

Supplementary Table 3. Independent predictors of HRQL scores in patients with cirrhosis and refractory ascites.

Outcome	Predictor	Beta	Std.Err.	p
Physical Functioning at Screening	ALD etiology	-16.17	7.16	0.0279
Physical Functioning at Month 6	CPT class C	-44.37	11.77	0.0010
Role Physical at Month 3	ALD etiology	19.70	7.20	0.0087
Bodily Pain at Month 3	alfapump® system	23.92	8.07	0.0048
Bodily Pain at Month 3	Age, per year	1.44	0.47	0.0034
Bodily Pain at Month 6	MELD score, per 1 point	-4.97	1.42	0.0018
General Health at Screening	Male gender	-15.69	5.70	0.0080
General Health at Month 1	Hepatorenal syndrome	14.17	6.02	0.0225
Vitality at Month 3	alfapump® system	12.24	6.29	0.0500
Vitality at Month 3	ALD etiology	18.19	6.93	0.0117
Vitality at Month 6	Age, per year	-0.96	0.35	0.0105
Vitality at Month 6	CPT class C	-44.33	9.42	0.0001
Social Functioning at Month 1	Urinary tract infection	33.33	13.98	0.0209
Social Functioning at Month 3	ALD etiology	24.46	7.54	0.0022
Social Functioning at Month 6	MELD score, per 1 point	-4.85	1.63	0.0062
Mental Health at Screening	Male gender	-15.86	6.65	0.0206
Mental Health at Month 6	Age, per year	-1.32	0.43	0.0053
Mental Health at Month 6	CPT class C	-28.89	11.75	0.0215
Physical Summary Score at Month 1	alfapump® system	4.73	1.91	0.0168
Physical Summary Score at Month 6	MELD score, per 1 point	-1.23	0.47	0.0154
Mental Summary Score at Screening	Male gender	-8.45	3.48	0.0184
Mental Summary Score at Month 6	Age, per year	-0.45	0.21	0.0399
Mental Summary Score at Month 6	CPT class C	-13.71	5.68	0.0241
SF-6D utility at Month 6	CPT class C	-15.80	6.61	0.0273
Abdominal Symptoms at Month 1	alfapump® system	1.09	0.47	0.0248
Abdominal Symptoms at Month 3	alfapump® system	0.92	0.44	0.0403
Abdominal Symptoms at Month 6	CPT class C	-1.97	0.88	0.0340
Activity at Month 3	alfapump® system	1.26	0.33	0.0005
Activity at Month 3	Male gender	1.85	0.46	0.0002
Activity at Month 3	Urinary tract infection	1.75	0.63	0.0083
Activity at Month 3	Variceal hemorrhage	0.94	0.38	0.0172
Activity at Month 6	alfapump® system	1.01	0.38	0.0136
Activity at Month 6	Urinary tract infection	1.34	0.60	0.0350
Emotional Function at Month 6	MELD score, per 1 point	-0.26	0.07	0.0017
Fatigue at Month 3	alfapump® system	0.92	0.37	0.0171
Fatigue at Month 3	ALD etiology	0.79	0.41	0.0603
Fatigue at Month 6	MELD score, per 1 point	-0.21	0.06	0.0019
Systemic Symptoms at Month 1	alfapump® system	0.88	0.28	0.0027
Systemic Symptoms at Month 3	Variceal hemorrhage	0.64	0.34	0.0672
Systemic Symptoms at Month 6	MELD score, per 1 point	-0.15	0.07	0.0288
Worry at Month 6	MELD score, per 1 point	-0.26	0.09	0.0091
Total CLDQ at Month 1	alfapump® system	0.53	0.23	0.0268
Total CLDQ at Month 3	Variceal hemorrhage	0.60	0.32	0.0659
Total CLDQ at Month 6	MELD score, per 1 point	-0.18	0.05	0.0017