Editorial

This year’s International Liver Congress was very special for the team at Sequana Medical. Not only were the first results of the much anticipated randomised controlled trial presented by Prof. Rajiv Jalan in General Session 3, but we were proud to be Silver Sponsors of the congress and to host our own satellite symposium, where leading hepatologists Prof. Berg, Prof. De Gottardi and Prof. Jalan presented the very latest clinical data on the alfa pump system. I would like to take the opportunity to extend my heartfelt thanks to the speakers for their informative and engaging presentations.

In this special ILC Highlights newsletter, we bring you a summary and key take-aways from the symposium presentations as well as an update on clinical studies, post-PIONEER experience and our congress schedule.

This is an exciting time for the alfa pump system, in terms of both the availability of new data and adoption of the new therapy into daily clinical use. We truly appreciate the support we receive from all of our customers and colleagues in the medical community, and look forward to seeing you at next year’s ILC in the beautiful city of Amsterdam, or at one of the many other congresses we will be attending throughout the year.

Yours,

Stephen McGill,
Chief Commercial Officer

Symposium Summary
Satellite Symposium
Therapeutic Advances in Refractory Ascites

Chair: Prof. Thomas Berg

Speakers:

alfa pump vs. Standard of Care in ascites treatment – RCT results
Prof. Rajiv Jalan,
Royal Free Hospital, London, UK

‘Real World Data’ for the alfa pump system
PD Dr. Andrea De Gottardi,
Inselspital Bern, Switzerland

TIPS or alfa pump? That is the question
Prof. Thomas Berg,
University of Leipzig, Germany
**alfa**pump® system vs. Large Volume Paracentesis in the treatment of refractory ascites: A Multicentre Randomised Controlled Study – Prof. Rajiv Jalan

Professor Jalan presented the first results from the much anticipated randomised controlled trial (RCT). His presentation began with a short introduction to the problem of ascites and the key efficacy data on **alfa**pump from the pivotal PIONEER trial\(^1\). He went on to describe the RCT, a multicentre, open, randomised, and controlled trial in 6 European centres, including 60 adult patients with refractory ascites who were randomised to either the **alfa**pump system or Standard of Care (SoC) of therapeutic large volume paracentesis (LVP). The primary objective was 6-month paracentesis-free survival defined as the time to first LVP at 5 litres or above. Secondary objectives included the need for paracentesis, cirrhosis-related complications, safety and survival and nutrition, which were discussed in the presentation. Further objectives still under analysis include quality of life.

**Efficacy**

Time to first LVP was significantly longer in the **alfa**pump group. Only 10 of the **alfa**pump patients required an LVP during the study, with an average of 1.1 events per patient in the **alfa**pump group, versus 8.6 per patient in the SoC group (Fig 1). Furthermore, there were significantly fewer LVPs in the **alfa**pump group than in the SoC group (30 vs. 268) (Fig 1). The primary reasons for paracentesis in the **alfa**pump group were pump and catheter issues and programming of the pump system which was too low for the amount of ascites being produced, with 70% of the LVPs occurring in 4 patients.

Professor Jalan also presented results from the Royal Free Hospital sub-study\(^2\) on nutrition (Fig 2). Again, the results in this patient cohort were very encouraging, demonstrating a statistically significant improvement in nutrition in **alfa**pump patients compared to SoC as measured by change from baseline in mid-arm muscle circumference (MMAC) and handgrip.

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\(^1\) Large Volume Paracentesis (LVP)

**AP:** **alfa**pump system  
**SoC:** standard of care  
**LVP:** large volume paracentesis not including pump-paracentesis

![Bar chart](Figure 1 – Number of LVPs in each group)

- **Mean number of LVP events per subject:**  
  - **AP:** 1.1  
  - **SoC:** 8.6

- **Total number of LVP (n=298):**  
  - **AP:** 30  
  - **SoC:** 268

- *p<0.001

Key secondary p-values are tested in accordance with Bonferroni-Holm.

\(^\dagger\) Annualised incidence rate not equivalent to the mean number of events predicted for one year of follow-up.
Safety

Overall, there were 31 cases of acute kidney injury (AKI) in the RCT. Of these, 27 were stage 1 and 4 were stage 2. In the alfpump group, 18 AKIs were stage 1, and one was stage 2. Most of these AKIs occurred within 7 days of implant and were transient in nature. In the SoC group, there were 9 stage 1 AKIs and 3 stage 2 AKIs. In the alfpump group 74% of all AKIs fully recovered, versus 33% in the SoC group. There was no additional risk of infection noted in the alfpump group as infection adverse events including peritonitis or urinary tract infection were similar in both groups. The study also demonstrated no significant difference in survival between groups at 6 months, which was approximately 70-80%. There were a total of 9 reinterventions during the study, including 3 device explants (11%). No subjects were discontinued due to device deficiency or need for reintervention, and all issues leading to re-intervention were easily corrected. For more information, see the abstract at [http://ilc-congress.eu/ilc-2016-ebooks/](http://ilc-congress.eu/ilc-2016-ebooks/). The full publication is expected later in 2016.

Figure 2 – Improvements in nutrition in the alfpump group

Dots represent individual data, lines represent medians, reference lines are overall median at baseline.
Real world data from the post-marketing surveillance registry (PMSR) – Prof. Andrea De Gottardi

Professor Andrea De Gottardi gave a first glimpse of ‘real world’ alfa pump data from the post-marketing surveillance registry (PMSR). This presentation reviewed the first 56 patients who completed at least one year of follow-up. The primary objective was to monitor the safety of the alfa pump system by collecting and reviewing all serious adverse events and device deficiencies, and secondary objectives included assessment of the clinical performance of the alfa pump system, assessment of the clinical impact of the alfa pump system, and assessment of usability.

This registry also demonstrated excellent effectiveness of the alfa pump. The mean number of paracenteses decreased from 2.9 per month at baseline (pre-implant) to just 0.3 (Fig 3). There were 56 LVPS in total, affecting 34% of participants – the remaining 66% remained LVP-free throughout the registry. Interestingly, the number of LVPs per patient decreased steadily by year throughout the study, illustrating a potential ‘learning curve’ effect since the beginning of the technology launch (Fig 4).
The majority of patients (61%) required no further surgical reintervention. Reinterventions were mainly catheter-related and were easy to manage. A total of 17 pumps were explanted due to adverse events (including infection or suspected infection). Other pumps (10) were explanted because the patient went on to liver transplantation or the pump was no longer necessary (patient stopped producing ascites). Finally, the usability of the alfapump was assessed, scoring highly in every category (Fig 5). The full publication is expected later in 2016.

### Usability: Feedback From Users

<table>
<thead>
<tr>
<th>Question</th>
<th>Score out of 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1: It was easy to find correct placement for charging</td>
<td>4.38</td>
</tr>
<tr>
<td>Q2: It was easy to maintain the correct charging position</td>
<td>4.5</td>
</tr>
<tr>
<td>Q3: The charging procedure to charge the Smart Charger is easy to perform</td>
<td>4.75</td>
</tr>
<tr>
<td>Q4: It was easy to identify the charging coil and start-stop button to begin charging</td>
<td>4.88</td>
</tr>
<tr>
<td>Q5: It was clear when the alfapump was fully charged</td>
<td>4.75</td>
</tr>
<tr>
<td>Q6: Battery levels of the alfapump and Smart Charger were clear and easy to understand</td>
<td>4.625</td>
</tr>
<tr>
<td>Q7: It was easy to verify that the battery level of the Smart Charger was above 50%</td>
<td>4.5</td>
</tr>
<tr>
<td>Q8: It was easy to verify the battery level of the alfapump</td>
<td>4.5</td>
</tr>
<tr>
<td>Q9: Charger Display messages on the Smart Charger were clear and easy to understand</td>
<td>4.25</td>
</tr>
</tbody>
</table>

Figure 5 – *Usability feedback from users*
Professor Berg held a fascinating lecture on the role of TIPS in the treatment of patients with refractory ascites, and how alfa pump might be valuable in this patient cohort. TIPS has a number of benefits including reducing portal hypertension, improving systemic hemodynamics and renal function. TIPS may also improve survival although the literature on this is divided. TIPS is, however, associated with a number of complications including hepatic encephalopathy, technical complications and blockages, and liver failure. So while TIPS implantation is an acceptable choice for a number of selected patients with refractory ascites, its applicability is restricted to patients with relatively preserved liver function. Furthermore, studies have shown that the re-occurrence rate for ascites after TIPS is over 40%.

Consequently, Prof. Berg has initiated the investigator-led AGUA trial, a randomised controlled study comparing the effectiveness of TIPS to the alfa pump system in controlling ascites over 2 years. A schematic is shown below (Fig 6). The primary objective is effectiveness of alfa pump in comparison with TIPS in controlling ascites. Secondary objectives include overall- and transplant-free survival, cumulative incidence of device defects / explants, quality of life, nutritional aspects, and quantity of albumin substitution.
The alfa pump system

- is safe and effective
- significantly reduces the need for paracentesis and improves nutrition in refractory ascites patients
- does not lead to any additional risk of infection or impact survival
- is well accepted by patients
- requires no reintervention in the majority of patients
The **alfa**pump System - **ILC Highlights 2016**

**alfa**pump: History Overview

**2000**
Original idea for an automated pump to remove ascites

**2005**
First prototype validated in pre-clinical testing

Since 2008, **alfa**pump has removed more than 75,000 litres of ascites in patients

**sequana**medical
Reinterventions: Post-PIONEER Experience

The graph below (Fig 7) shows the percentage of all implanted systems, either commercial or part of a clinical trial, that required a surgical reintervention from 2012 to 2015\(^5\). The annual reintervention rates decreased from 41.5% in 2012 to 18.7% over the time period, demonstrating the learning-curve effect associated with the alfa pump implantation at technology launch. Reinterventions include catheter blockages, migrations or dislocations, pump malfunctions, wound dehiscence and ascitic fluid leakage.

![Figure 7 – Percentage of reinterventions per year](image-url)
Further clinical trials

Sequana Medical is committed to working with the scientific community to produce clinical data for the alfa pump system. Below is a list of on-going trials.

### Sequana Medical sponsored trials

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Principal Investigator</th>
<th>ClinicalTrials.gov Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>alfa pump System Post Marketing Surveillance Registry (2011-AAR-004)</td>
<td>Prof. Andrea De Gottardi, Inselspital Bern, Switzerland</td>
<td>NCT01532427</td>
</tr>
<tr>
<td>A (M)Ulti-center, Prospective, (O) Pen Label, Uncontrolled Feasibility (S)Tudy to Assess the Safety and Effectiveness of an Automatic Low Flow (A)Scites (alfa) Pump (I)n Patients With (C)Irhosis and Refractory or Recurrent Ascites (MOSAIC)</td>
<td>Prof. Patrick Kamath, Mayo Clinic, Rochester, MN, USA</td>
<td>NCT02400164</td>
</tr>
<tr>
<td>alfa pump – albumin replacement therapy</td>
<td>Prof. Rajiv Jalan, Royal Free Hospital, London, UK</td>
<td>NCT02448160</td>
</tr>
<tr>
<td>Effects of Treatment of Ascites by the alfa pump System on Renal and Circulatory Function</td>
<td>Prof. Pere Gines, Hospital Clinic, Barcelona, Spain</td>
<td>NCT01438970</td>
</tr>
</tbody>
</table>

### Investigator-led trials

<table>
<thead>
<tr>
<th>Trial Name</th>
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</tr>
</thead>
<tbody>
<tr>
<td>alfa pump System Versus Transjugular Intrahepatic Portosystemic Shunt and Paracentesis in the Treatment of Ascites</td>
<td>Prof. Thomas Berg, University of Leipzig, Germany</td>
<td>NCT02612519</td>
</tr>
</tbody>
</table>
We will be exhibiting at the following congresses and events.

**Stop by and say hello!**

**2016**

**3rd – 4th June**
25. Kongress der Mitteldeutschen Gesellschaft für Gastroenterologie - Meiningen

**17th June**
11ème Journée Medico-Chirurgicale de Pathologie Digestive d’Amiens

**7th – 9th Sept**
BASL - Annual Meeting 2016 - Manchester

**22nd – 23rd Sept**
Annual Meeting SGG - SGVC - SALS 2016 - Interlaken

**21st – 24th Sept**
Viszeralmedizin 2016 - DGVS / DGAV - Hamburg

2. Poster PO187 ILC 2015 Vienna, Adebayo et al - Cardiac, Haemodynamic, Renal and Nutritional effects of the *alfa* pump® in cirrhotic patients with refractory ascites: A randomised study.

3. KDIGO definition AKI stage 1: serum creatinine 1.5–1.9 times baseline, or ≥0.3 mg/dl (≥26.5 mmol/l) increase, or urine output of < 0.5 ml/kg/h for 6–12 hours.

4. KDIGO definition AKI stage 2: serum creatinine 2.0–2.9 times baseline or urine output of <0.5 ml/kg/h for ≤12 hours.