Safety and Efficacy of the Extracorporeal Liver Assist Device (ELAD®) in Patients with Acute on Chronic Liver Failure

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ABSTRACT

Background: Patients with acute-on-chronic liver failure (ACLF) have limited treatment options, leading to significant morbidity and mortality. The Extracorporeal Liver Assist Device (ELAD) circulates patient plasma through a hollow fiber cartridge containing metabolically active, immortalized C3A human liver cells. Prior multicenter Phase 1 and 2 studies have indicated clinical utility in patients with Acute Liver Failure, and a study demonstrated significant improvement in transplant-free survival (TFS) in Chinese patients with ACLF.
Aim: Multicenter, Phase 2, open-label, randomized, concurrent control study to evaluate the safety and efficacy of the ELAD® bioartificial liver support system in ACLF patients. Efficacy endpoints included TFS and overall survival (OS) at 30 and 90 days
Methods: Adults with acute decompensation of cirrhosis, SOFA score ≥ 9 at screening, and either a MELD score of ≥32, or MELD ≥24 and at least one of;
a. Encephalopathy – West Haven grade 3 or 4;
b. Type-1 hepatorenal syndrome.
Subjects were randomized 2:1 to either standard medical therapy (SMT) PLUS continuous ELAD treatment (SMT+ELAD) or SMT alone.
Results: Eighteen (18) patients with ACLF were randomized to SMT+ELAD (n=14) or SMT (n=4). One patient randomized to SMT+ELAD was ineligible at baseline and never treated. Mean MELD scores were 34.3 +/- 5.7 and 40.8 +/- 5.1 (p=.08), respectively. ELAD treatment ranged from 36-240 hours (mean=122.8 ± 21.7). More patients achieved 30-day TFS in the SMT+ELAD group (23%) versus SMT (0%). There was no difference in 30-day OS (SMT+ELAD 46% vs SMT 50%). 90-day OS was improved for SMT+ELAD (39%) vs SMT (25%) as was 90-day TFS (SMT+ELAD 15% vs SMT 0%). The rate of liver transplantation was higher for SMT (75%) vs SMT+ELAD (23%). ELAD treatment was well tolerated; of 39 SAEs reported (SMT+ELAD=32, SMT=7), none were unexpected for an extracorporeal device. In 2 patients SAEs thought to be possibly related to ELAD treatment led to discontinuation of ELAD.
Conclusion: SMT+ELAD in ACLF improves TFS at 30 and 90 days and OS at 90 days, is safe and well-tolerated. A larger, sufficiently powered randomized controlled trial is currently underway to expand on the results of this Phase 2 study.

OBJECTIVE

Assess ELAD safety and efficacy in a multicenter, Phase 2, open-label, randomized, concurrent control study in Acute on Chronic Liver Failure ACLF patients.

HYPOTHESIS

- **ELAD is safe in a population of US ACLF patients**
- **Preliminary efficacy results will help define a pivotal study in this patient population**

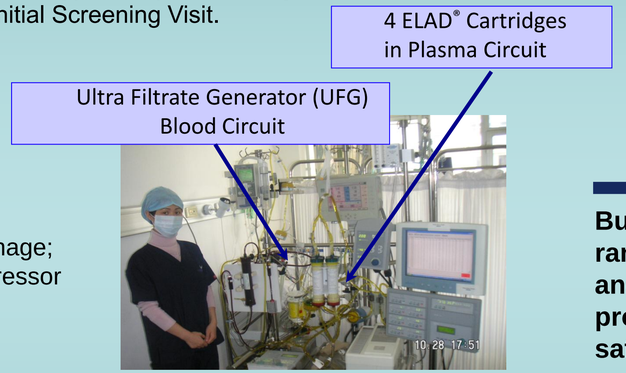
METHODS

Key Inclusion Criteria

- Acute decompensation of cirrhosis over the preceding 48-72 hour period;
- Up to 4 weeks from symptom onset to presentation;
- Presence of a precipitating event;
- Either a MELD score of ≥32, or ≥24 with one or more of the following;
  - Severe encephalopathy of grade 3 or 4 by the West Haven criteria;
  - Renal dysfunction typical of type-1 hepato-renal syndrome;
  - SOFA score ≥9 at the initial Screening Visit.

Key Exclusion Criteria

- Platelets <50,000;
- Chronic renal failure;
- Contraindication to renal replacement therapy;
- Uncontrolled sepsis;
- Evidence of major hemorrhage;
- Escalating need for vasopressor support.



CONCLUSIONS

- **Primary objectives met**
  - **ELAD was well tolerated – safety data similar to control;**
  - **Survival data encouraging – 90 day OS, 30 and 90 day TFS improved in ELAD patients vs controls**
- **Outcome impacted pivotal study design**
  - **Enroll patients with fewer complications;**
  - **Enroll patients with lower MELD scores;**
  - **Use *"prevention of disease progression" prior to* transplant/ death as primary endpoint.**

FUTURE DIRECTIONS

Building on these phase 2 results, a larger multicenter, randomized, controlled pivotal trial is now underway in USA, EU and Middle East with an improved trial design based on a progression end point and sufficiently powered to confirm safety and efficacy.

RESULTS

EFFICACY

	ELAD (N=14)*	Control (N=4)**
Mean MELD (+/-SD)	34.3 (+/-5.7)	40.8(+/-5.1)
Transplant rate	23%	75%
Survival		
30 day overall	46%	50%
90 day overall	39%	25%
30 day transplant-free	23%	0%
90 day transplant-free	15%	0%

SAFETY

	ELAD (N=14)	Control (N=4)	Total (N=18)
No. of AEs	211 (13 pts)* 16 AE/pt	87 (3 pts)** 29 AE/pt	298 (16 pts)
No. of SAEs	32 (10/13 pts) 3 SAE/pt	7 (1/3 pt) 2 SAE/pt	39 (11 pts)
No. of Pts. who Discontinued ELAD Due to AE	2 (14.3%)	0 (0%)	2 (11.1%)
No. of Pts with ELAD-related AEs			
Possible	9 (64.3%)	0 (0%)	9 (64.3%)
Probably	4 (28.6%)	0 (0%)	4 (28.6%)

*1 ELAD subject ineligible at Baseline and not treated **1 Control subject withdrew after randomization