A RANDOMIZED, OPEN-LABEL, MULTICENTER, CONTROLLED STUDY TO ASSESS SAFETY AND EFFICACY OF ELAD®, A HUMAN CELL-BASED BIO-ARTIFICIAL LIVER SUPPORT SYSTEM, IN SUBJECTS WITH ALCOHOL-INDUCED LIVER DECOMPENSATION (AILD)

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VITAL THERAPIES® TARGETING LIVER DISEASE

BACKGROUND

Treatment options for patients with AILD are limited, leading to significant morbidity and mortality. ELAD® is designed to provide liver support continuously for up to 10 days to a subject with compromised liver function and allow time for the native liver to regenerate by circulating patient plasma through a hollow fiber cartridge containing metabolically-active, immortalized VTL C3A human liver cells.

STUDY OBJECTIVE

Based on preliminary findings from a subset of subjects with AILD enrolled in a prior Phase 2 study (VTI-206), the aim is to provide data on the safety and clinical utility of ELAD in a larger, prospectively-defined population with AILD. The primary endpoint will evaluate overall survival of subjects with a clinical diagnosis of AILD up to at least Study Day 91. The secondary objectives are to determine the proportion of survivors at Study Days 28 and 91. Exploratory objectives are to evaluate the ability of ELAD to stabilize liver function, measured using the Model of End-stage Liver Disease (MELD)-based time to progression (TTP) up to Study Day 91, and the proportion of progression-free survivors (PFS) up to Study Days 28 and 91. The objective of this poster is to provide an overview of study enrollment and study population characteristics for this randomized trial.

MATERIALS & METHODS

Eligibility requirements (Table 1) were established in order to replicate the AILD population in VTI-206. Target age based on the VTI-206 population is 45-55 and baseline target MELD is 27-29 for the current study. A total of 200 evaluable subjects meeting these requirements will be randomly assigned in a 1:1 ratio to receive either standard of care treatment for AILD plus treatment with the ELAD System (ELAD group) or standard of care of treatment for AILD alone (Control group). ELAD treatment will take place for a maximum of five 24-hour periods unless any of the discontinuation criteria are met. It was anticipated that enrollment would take approximately 2 years.

Table 1. Key inclusion/exclusion criteria

Inclusion criteria

1. Age ≥ 18 years;
2. Total bilirubin ≥ 8 mg/dL;
3. A clinical diagnosis of alcohol-induced liver decompensation (AILD), based upon evidence (by lab test, medical history or family interview) or a clinical judgment of a temporal (6 weeks or less) and causal relationship between use of alcohol and this onset of symptoms;
4. Subjects meeting inclusion criteria 1 through 3 will be classified as having either:
   a. Severe acute alcoholic hepatitis (AAH), with:
      i. Medical history of alcohol abuse; AND
      ii. Maddrey score of ≥ 32; AND
      iii. AAH documented by either:
         1. Confirmatory liver biopsy, OR
         2. Two or more of the following:
            a. Hepatomegaly,
            b. AST > ALT,
            c. Ascites,
            d. Leukocytosis (WBC count above lab normal at site), OR
   b. Alcohol-induced decompensation of chronic liver disease that is *not* acute alcoholic hepatitis (as defined above), with:
      i. MELD score of 18-35; AND
      ii. Underlying chronic liver disease documented by:
         1. Liver biopsy, AND/OR
         2. Laboratory findings, AND/OR
         3. Medical history;
5. Not eligible for liver transplant during this hospitalization;

Exclusion criteria

1. Platelet count < 40,000/mm3;
2. International Normalization Ratio (INR) > 3.5;
3. MELD Score > 35;
4. AST > 500 IU/L;
5. Evidence of infection unresponsive to antibiotics;
6. Evidence of reduction in total bilirubin of 20% or more in the previous 72 hours, if available. Bilirubin measurements must be taken at least 12 hours after any procedure known to artificially alter serum bilirubin (e.g., administration of packed red blood cells, plasma exchange);
7. Evidence of hemodynamic instability;
8. Evidence of active bleeding or of major hemorrhage defined as requiring ≥ 2 units packed red blood cells to maintain a stable hemoglobin occurring within 48 hours of Screening;
9. Previous liver transplant;
10. Clinical evidence of liver size reduction due to cirrhosis (liver size of the craniocaudal diameter [sagittal view] < 10 cm when measured on the mid clavicular line (or equivalent measurement) by ultrasound, or liver volume < 750 cc as determined by CT), unless Investigator interpretation of the clinical evidence indicates liver size of < 10 cm or volume < 750 cc is not considered reduced for the individual subject;
11. Subject has chronic end-stage renal disease requiring chronic hemodialysis for more than 8 weeks (not classified as hepatorenal syndrome);
12. Have a Do Not Resuscitate or a Do Not Intubate (DNR/DNI) directive (or such local equivalent) or any other Advanced Directive limiting Standard of Care in place (the DNR/DNI criterion is not applicable in the UK);

RESULTS

Graph 1. # of subjects enrolled by site

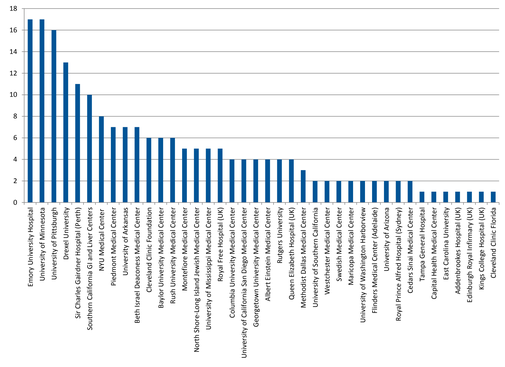

Table 2. The top 10 sites by enrollment:

Site Name	Subjects Enrolled
University of Minnesota	17
Emory University	17
University of Pittsburgh	16
Drexel University	13
Sir Charles Gairdner Hospital-Perth	11
Southern California GI and Liver Center	10
NYU Medical Center	8
Beth Israel Deaconess Medical Center	7
University of Arkansas	7
Piedmont Atlanta Hospital	7

Table 3. Baseline demographics

Parameters		n
Age – Mean±SD (range, unit)	45.6±10.0 (25, 68, years)	202
Gender Male - n (%)	118 (59%)	200
Female - n (%)	82 (41%)	200
Race White - n (%)	173 (86.5%)	200
Other - n (%)	27 (13.5%)	200
HE stage 0 - n (%)	103 (53.4%)	193
HE stage 1&2 - n (%)	77 (39.9%)	193
HE stage 3&4 - n (%)	13 (6.7%)	193
Liver Size – Mean±SD (range, unit)	19.1±4.4 (10, 29, cm)	171
Mean/Median time since enrollment (as of May 1, 2015)	374/360 days	203

Table 4. Baseline labs

Parameters	Mean	SD	n
MELD	27.2	3.8	196
MADDREY	72.9	25.0	197
PT (secs)	22.4	5.2	198
INR	2.0	0.5	196
Total Bilirubin (mg/dl)	25.0	9.2	196
Direct Bilirubin(mg/dl)	16.0	7.3	165
Creatinine (mg/dl)	1.0	0.7	196
ALB (g/dl))	2.7	0.7	196
ALT (IU/L)	61.8	42.3	198
AST (IU/L)	134.7	73.8	196
Sodium (mmol/l)	133.9	5.5	198
WBC ($X10^3/mm^3$)	14.5	7.4	198
HCT (%VOL)	29.5	5.9	197
PLT ($X10^3/mm^3$)	152.5	82.4	196

SUMMARY

The first subject was enrolled in March 2013 and enrollment was completed in January 2015. A total of 203 subjects were enrolled in 40 clinical sites in the United States, Europe and Australia (Graph 1) and the top ten enrollers are listed in Table 2. Based on data captured as of February 10, 2015 in the electronic data capture system for the study, the investigated population mainly comprised white (86.5%) males (59.0%). The age ranged from 25 to 68 years (mean= 45.6 years, SD=10.0 years, n=202). Hepatic encephalopathy was observed in 46.6% subjects at enrollment (Table 3). Major baseline laboratory variables include: MELD (27.2±3.8, n=196), Maddrey (72.9±25.0, n=197), bilirubin (25.0± 9.2 mg/dl, n=196), INR (2.0±0.5, n=196), creatinine (1.0±0.7 mg/dl, n=196), PT (22.4±5.2 seconds, n=198), ALT (61.8± 42.3 IU/L, n=198), AST (134± 73.8 IU/L, n=196), sodium (133.9± 5.5 mmol/l, n=198), WBC (14.5±7.4 $X10^3/mm^3$, n=198), etc. (Table 4).

DISCUSSION

Study power assumptions included defining a 90-day control survival rate of approximately 50% and a study treatment arm survival improvement of approximately 20%, consistent with findings from prior studies. According to the AAH-MELD calculator[1] a MELD of 27.2 translates to a 90-day survival rate of 49%. A recent study of sAAH subjects in the UK (the STOPAH trial[2]) enrolled a less sick subject population (mean baseline MELD ~22) which was reflected in a 90-day survival of approximately 72%, also consistent with the MELD calculator (69%), irrespective of treatment arm (prednisolone, pentoxifylline, the combination or placebo).

CONCLUSIONS

Trial enrollment has proceeded in accordance with the anticipated timelines. Average age and MELD score at baseline are within the trial target ranges established during VTI-206. Baseline data characterize a group of subjects with alcohol-induced liver decompensation.

REFERENCES

1.MELD score and 90-day mortality rate for alcoholic hepatitis. MAYO clinic. http://www.mayoclinic.org/. Accessed on 10Feb2015.
2.M.R. Thursz, et al. Steroids or Pentoxifylline for Alcoholic Hepatitis: Results of the STOPAH Trial. AASLD. 2014.

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