Synopsis

Name of Sponsor:	Vital Therapies, Inc.
Name of Finished Product:	ELAD®
Name of Active Ingredient:	C3A cells

Number and Title of Study:

VTI-206: Efficacy and Safety of ELAD® in Subjects with Acute on Chronic Hepatitis (AOCH)

Investigators Who Enrolled Subjects and Study Centers by Country:

United States

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61: Santiago Munoz, MD, Temple University Hospital, Philadelphia, PA
62: Paul Kwo, MD, Indiana University, Indianapolis, IN
63: Fred Poordad, MD, Cedars Sinai Medical Center, Los Angeles, CA
65: Helen Te, MD, University of Chicago Medical Center, Chicago, IL
66: David Kaufman, MD, Strong Memorial Hospital, Rochester, NY
68: Rasheed Balogun, MD, Department of Medicine, Nephrology Division, University of Virginia Health System, Charlottesville, VA
69: Donald Hillebrand, MD, Scripps Clinic, LaJolla, CA
73: Lewis Teperman, MD, NYU School of Medicine, NYU Langone Medical Center, New York, NY
75: Steven Conrad, MD, Emergency Medicine, Louisiana State University Health Sciences Center, Shreveport, LA
76: Robert Brown, MD, Center for Liver Disease and Transplantation, Columbia University Medical Center, New York, NY
80: James Trotter, MD, Baylor University Medical Center, Dallas, TX
81: David Wolf, MD, Division of Gastroenterology and Hepatobiliary Disease, Westchester Medical Center, Valhalla, NY
88: Abdullah Mubarak, MD, The Liver Institute at Methodist in Dallas and Plano, Dallas, TX

United Kingdom

77: Julia Wendon, MD, Institute of Liver Studies, Kings College London, London
78: Nick Murphy, Critical Care and Anaesthetics, Queen Elizabeth Hospital, Birmingham
82: Alistair Lee, MD: Department of Anesthetics, Royal Infirmary Edinburgh, Edinburgh
83: Andrew Austin, MD, Derby Digestive Diseases Center, Royal Derby Hospital, Derby
87: James O'Beirne, MD, The Sheila Sherlock Liver Center, Royal Free Hospital London, London

Denmark

86: Fin Stolze Larsen, MD, Hepatology Department, Rigshospitalet Denmark, Copenhagen

Saudi Arabia

79: Ahmed Al-Jabbar, MD, FRCPC, King Fahad National Guard Hospital, Riyadh

Publication: None at the time of this report

Study Period:	**Phase of Development:** 3
First subject enrolled: 25 September 2009 Notification of early study termination: 28 April 2011 Last subject completed Day 91: 23 June 2011	

Objectives:

As stated in the protocol, the objective was to evaluate the efficacy and safety of ELAD to stabilize liver function during the acute phase of AOCH.

Methodology:

This was a multicenter, open-label, randomized, concurrently-controlled study of subjects with AOCH, defined as acute decompensation of chronic liver disease over the preceding 28 days. Eligible subjects were randomly assigned in a 1:1 ratio to receive standard medical therapy for AOCH plus treatment with the ELAD system (ELAD group) or standard medical therapy alone (Control group). Subjects with AOCH could have a clinical diagnosis of what was termed in the protocol "acute alcoholic hepatitis (AAH)" but was in fact alcohol-induced liver decompensation (hereafter referred to as AILD). Subjects who did not have a diagnosis of AILD were described as "non-AAH" in the protocol and are hereafter referred to as "non-AILD." To ensure that the populations were balanced, there were separate randomization schedules for subjects with a clinical diagnosis of AILD vs non-AILD.

Subjects in the ELAD group received treatment with ELAD for a minimum of three and a maximum of five 24-hour periods, with a possible extension waiver to ten 24-hour periods if the Investigator believed it would be beneficial to the subject. The period of ELAD treatment was defined as the Treatment Period, the period from discontinuation of ELAD treatment to Day 28 as the Post-Treatment Period, and Days 29 to 91 as the Follow-up Period.

Subjects in the Control group received standard medical therapy throughout the study. For subjects in this group the first five 24-hour periods of the study (Day 1, Hour 0 to Day 6, Hour 0) were defined as the Treatment Period, Days 7 to 28 as the Post-Treatment Period, and Days 29 to 91 as the Follow-up Period.

Subjects in both groups were evaluated throughout the Treatment Period and the Post- Treatment Period. Vital status of all subjects was followed from Day 29 to Day 91 and all defined events were recorded.

Enrollment in the non-AILD cohort was suspended as of 31 January 2011 (Protocol Amendment 3) based on a recommendation of the Data Safety Monitoring Board (DSMB). Based on their review of safety data for the prospectively stratified diagnostic cohorts, the DSMB noted that the non-AILD group had a low rate of transplants that made it unrealistic to evaluate the efficacy of ELAD for "bridge to transplant" in that population. Based on a trend toward a better outcome in the AILD subjects and not for any safety concern, the DSMB recommended that enrollment should be limited to subjects with a diagnosis of AILD and that non-AILD subjects should either be excluded or enrollment confined to subjects waitlisted for transplant. Enrollment remained open for AILD subjects until 28 April 2011, when the Sponsor terminated enrollment so the results could be analyzed in detail and the findings applied to the design of subsequent protocols. Any enrolled subjects were to complete the remaining study visits through Day 91.

Number of Subjects (Planned and Analyzed):

Planned: 80

Randomized: 62 (29 ELAD, 33 Control); the only available data for 1 Control subject was survival so that subject is only included in data presentations for that endpoint

Analyzed:

Safety population: 61 subjects (29 ELAD, 32 Control)

Modified intent-to-treat (MITT) population (subjects who received treatment [excluding Baseline failures and subjects who withdrew consent] and had 90-day data): 51 subjects (24 ELAD, 27 Control)

Per-protocol (PP) population (MITT subjects who also received at least 72 hours of treatment): 45 subjects (19 ELAD, 26 Control)

Diagnosis and Main Criteria for Inclusion:

Diagnosis: AOCH

Main Inclusion Criteria (as of Protocol Amendment 1): age $\geq$ 18 and $\leq$ 67 years, acute decompensation of chronic liver disease over preceding 28 days, MELD score between 18 and 35 (inclusive), and diagnosis of AOCH (AAH or non-AAH; as noted above, referred to in this report as AILD or non-AILD).

Test Product, Dose and Mode of Administration, Batch Number:

Treatment with the ELAD system (using 4 cartridges each containing approximately 110 g of C3A cells through which the subject's plasma ultrafiltrate was circulated)

Duration of Treatment:

Three to five 24-hour periods of ELAD treatment, with a possible extension waiver to ten 24-hour periods if the Investigator believed it would be beneficial to the subject.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Both ELAD-treated and Control subjects received standard medical therapy (conventional therapy for AOCH determined to be clinically appropriate by the treating physician).

Criteria for Evaluation:

Efficacy: According to the protocol, time to progression (TTP) was planned as the efficacy parameter, with progression defined as the earlier of death or an increase of 5 points or more in MELD score at defined times post-baseline. However, as described below, 90-day overall survival was analyzed for efficacy. Transplant-free survival (TFS) was an exploratory analysis.

Safety: Adverse events (AEs), clinical laboratory evaluations, vital signs, and physical examinations

Statistical Methods:

For the original protocol-specified primary efficacy analysis, a Kaplan-Meier analysis was to be used to evaluate differences between treatment groups in TTP based on death or the first observed increase of at least 5 points from Baseline MELD score (whichever occurred earlier) at least 24 hours after the ELAD Treatment Period ended and up to Day 91 (90 days following Baseline).

As a result of the early study termination described above and in response to recommendations from the FDA, the 90-day overall survival analysis was determined to be the primary analysis and the planned TTP analysis based on MELD progression described in the protocol was not performed. Overall survival is considered to be a more robust and statistically conservative indicator of efficacy under these circumstances. Because of the DSMB findings that led to the study being terminated early, both MITT and PP populations were analyzed, with each considered equally valid.

Results:

Disposition and Demographics: Sixty-two subjects were randomized (29 ELAD, 33 Control). For 1 subject randomized to the Control group the informed consent was lost and the only information available (based on a serious adverse event [SAE] report provided to the Sponsor) was survival. That subject was therefore only included in data presentations for survival. Among the 29 subjects randomized to ELAD, 20 (69%) completed at least 3 days of ELAD treatment. Nine subjects randomized to ELAD either did not initiate treatment or had treatment discontinued after less than 3 days. Overall, age ranged from 32 to 68 years with a mean of 61 years, 38 (62%) subjects were male and 23 (38%) were female, 52 (85%) were white, and 53 (87%) were not Hispanic or Latino.

Efficacy:

The efficacy conclusions are as follows:

- The hazard ratios indicate that the risk of death over a similar period of time was 1.3 (MITT population) or 1.9 (PP population) times as great for AILD Control subjects as for AILD subjects treated with ELAD.
- Since there was an imbalance of the rate of transplant between non-AILD subjects in the ELAD and Control groups an exploratory analysis of TFS was carried out, which revealed no significant difference between the groups and no treatment benefit with ELAD.
- Since the AILD and the non-AILD ELAD-treated mean MELD scores were similar to those in the respective AILD and non-AILD Control subjects, this parameter did not appear to suggest any treatment benefit with ELAD.
- The mean Maddrey Scores in the AILD ELAD-treated subjects were consistently lower than those in the AILD Control subjects on almost all scheduled visits between Treatment Day 2 and Follow-up Treatment Day 56, suggesting that the disease severity was decreasing over time more in the AILD ELAD-treated subjects than in the AILD Control subjects. This trend was not observed in the non-AILD subjects.

Safety:

The safety conclusions with respect to the ELAD and Control groups were as follows:

- Most ELAD-treated (86%) and Control (75%) subjects reported at least one TEAE.
- The most frequently reported TEAEs in the ELAD-treated group tended to be clustered in the Blood and Lymphatic System Disorders and included anemia, coagulopathy, hypofibrinogenemia, and thrombocytopenia.
- Most of the TEAEs in the ELAD-treated and Control Subjects were moderate (38% in both groups) or severe (41% vs 34%).
- The incidence of ELAD-treated subjects who discontinued the study due to AEs was approximately 21% and due to SAEs was approximately 10%.
- The incidence of subjects experiencing SAEs in the ELAD-treated group (62%) was similar to the incidence in the Control group (53%).
- The most frequently experienced SAEs in the ELAD-treated group were sepsis (3 subjects), hepatic encephalopathy (2 subjects), and hepatic failure (2 subjects) while the most frequently experienced SAEs in the Control group were gastrointestinal hemorrhage (4 subjects), multi-organ failure (3 subjects), anemia (2 subjects), and cardio-respiratory arrest (2 subjects).
- SAEs considered to be related to ELAD, each for 1 subject, were hematemesis, renal failure/vaginal hemorrhage, gastrointestinal hemorrhage/sepsis, and intravascular hemolysis.
- The statistically significant differences between the mean diastolic blood pressures at Treatment Days 2, 4, 5, and 6 do not appear to be clinically significant since there was an imbalance between pre-treatment diastolic blood pressure in the ELAD and Control groups (the majority of ELAD-treated subjects had a pre-treatment diastolic blood pressure less than 60 mmHg while the majority of Control subjects had a pre-treatment diastolic blood pressure greater than 60 mmHg) and none of the changes from pre-treatment for diastolic blood pressures in the ELAD-treated and Control groups was statistically significant.
- None of the means or mean changes from pre-treatment for respiratory rate, systolic blood pressure, mean arterial pressure or temperature was clinically significant.

Conclusion:

Ninety-day overall survival analyses showed a statistically significant difference in the benefit of ELAD over Control between the two diagnostic cohorts, with AILD subjects showing a trend favoring ELAD over Control while non-AILD subjects showed the opposite trend. Based on these results, future studies will focus on subjects with similar characteristics to this AILD cohort. Beyond the overall survival efficacy results discussed above, the overall safety of ELAD therapy was generally not clinically different from the therapyt given to the Control group. Furthermore, the ELAD treatment appeared to be well tolerated.

Date of the Report: 5 February 2013