Early Intervention with Extracorporeal C3A Cellular Therapy in Patients with Alcoholic Hepatitis with MELD <28 May Result in Clinical Benefit and Less Need for Later Transplantation

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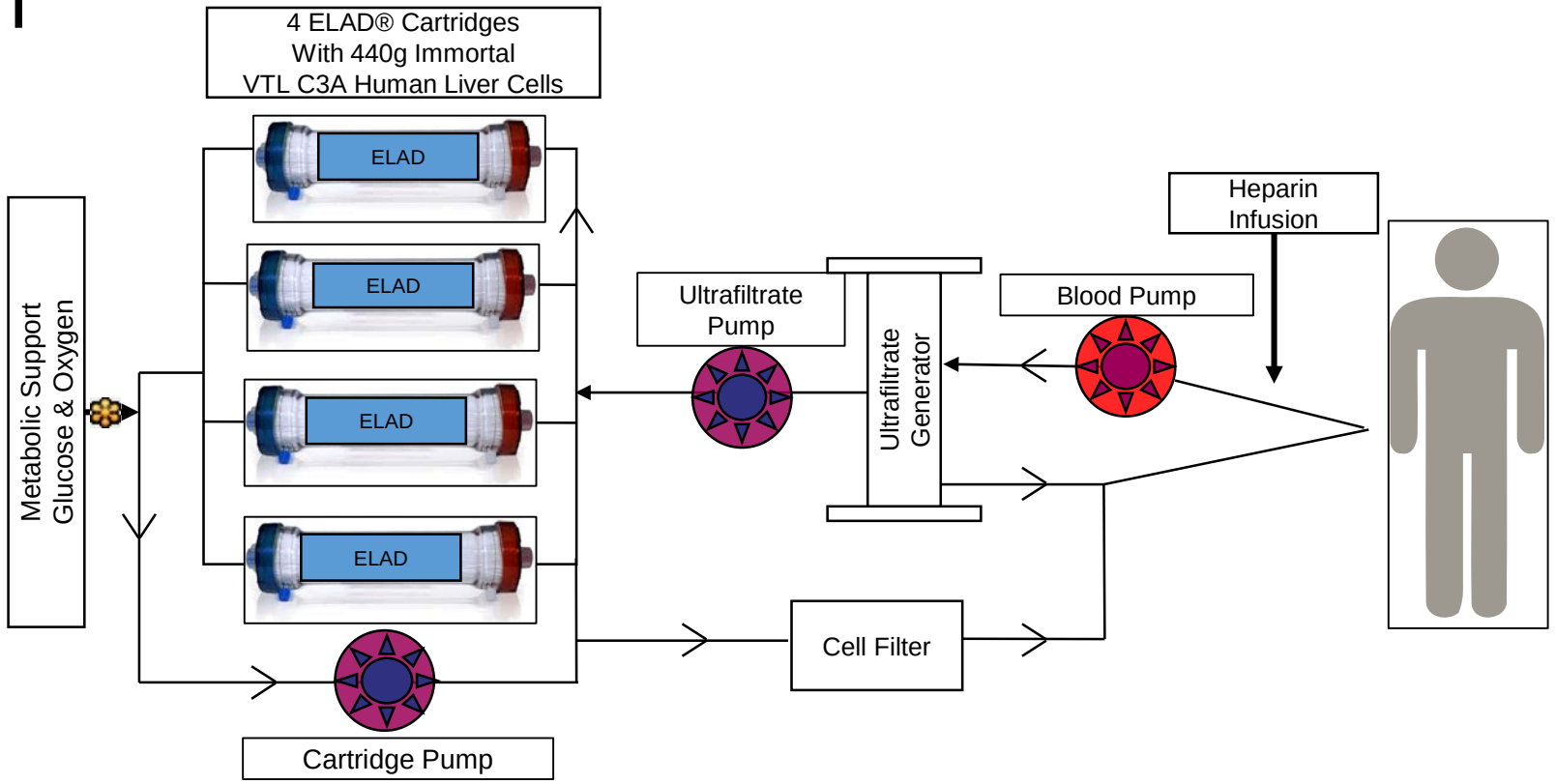
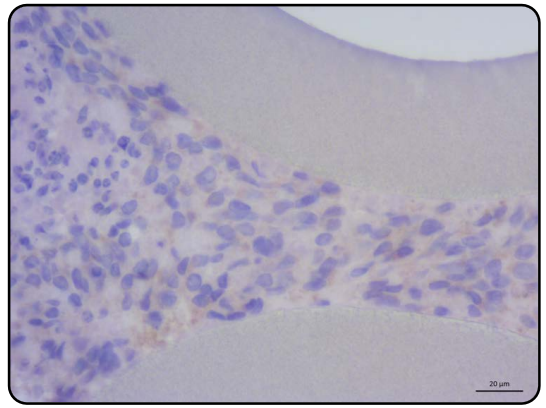
The ELAD System



VTL C3A Cells have been shown to produce:

- Anti-inflammatory proteins[1]
  - IL-1 receptor antagonist
  - Alpha-1-antitrypsin
  - Gelsolin
- Growth factors[2]
  - Amphiregulin
  - TGFα
  - VEGF
- Anti-apoptotic factors[2]
  - EGFR signaling ligands
- Coagulation factors[3]
  - Pro/anti-coagulation
  - Anti-fibrinolysis
- Cytochrome P450 isoenzymes[4]
  - e.g. CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5



References:
[1] Landeen, 2015, ILTS, P249
[2] Bedard, 2015, AASLD, P1770
[3] Riley, Experimental Biology, *in submission*
[4] Landeen, 2015, J Hepatology 62:S764

VTI-208:
Design and Major Inclusion / Exclusion Criteria

Design:

- International, prospective, randomized, controlled, open-label Phase III trial
- 200 subjects
- 1:1 randomization:
  - ELAD (5 days continuous therapy) plus protocol-mandated standard of care (SOC) or
  - SOC alone
- Weekly home health visits post-discharge
- Primary endpoint:
  - Kaplan-Meier analysis of overall survival
- Secondary endpoints:
  - Proportion of survivors at 28 and 91 days

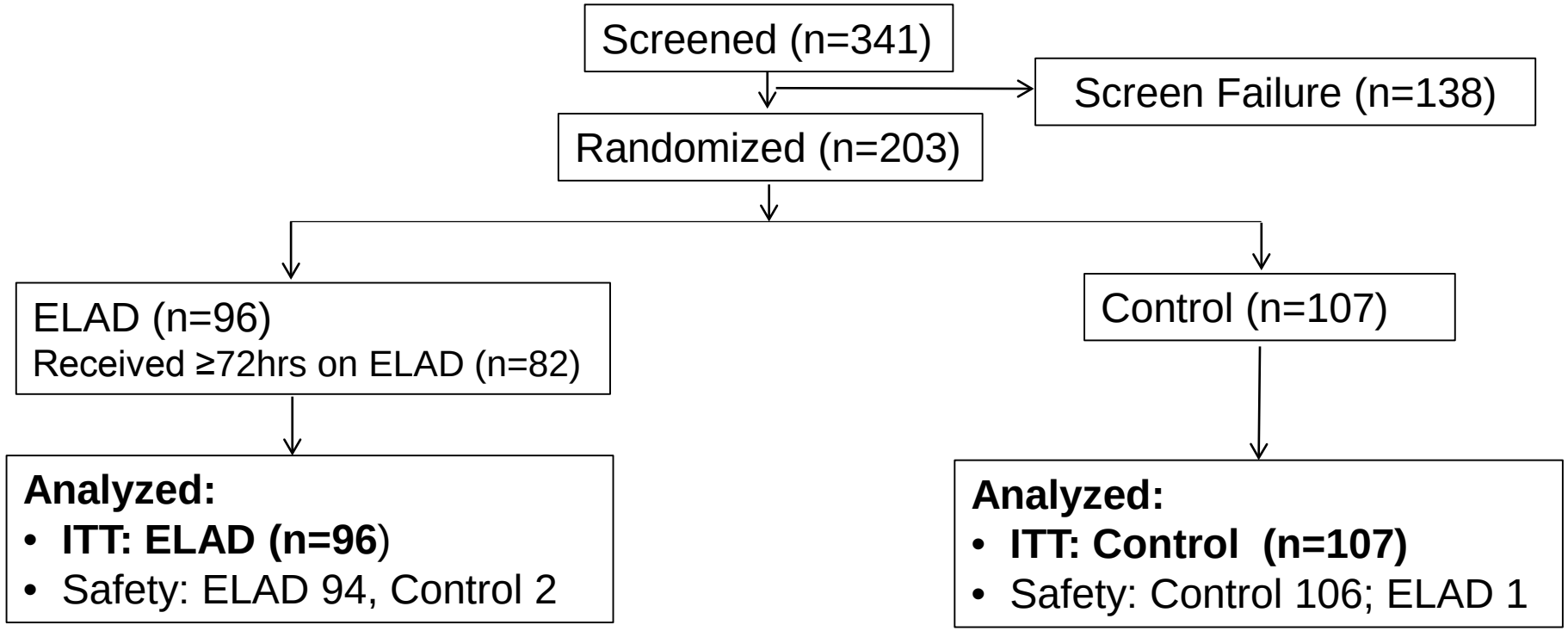
Inclusion

- Age >18
- Total bilirubin ≥8 mg/dL
- EtOH within 6 weeks of onset of symptoms
- Group A (sAAH)
  - Maddrey DF ≥32
  - Liver biopsy or
  - At least 2 out of:
    - Hepatomegaly
    - AST>ALT
    - Elevated WBC
    - Ascites
- Group B (AILD)
  - MELD 18 – 35
  - Histological / laboratory / medical evidence of underlying disease

Exclusion

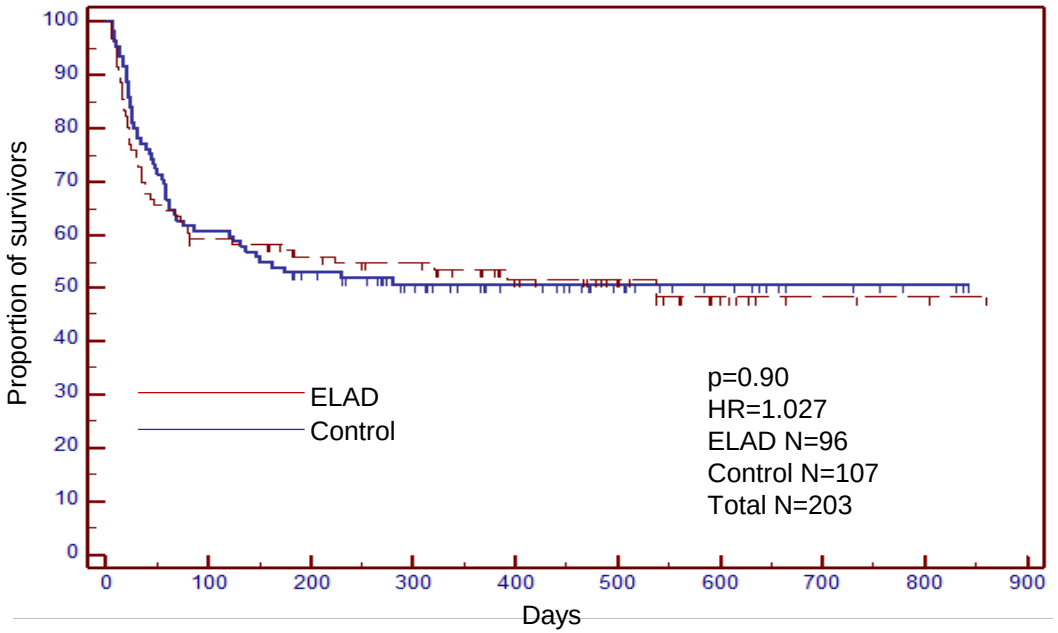
- Platelets <40,000/mm^3
- INR >3.5
- MELD >35
- AST >500 IU/l
- Bilirubin reduction of >20% in prior 72 hours
- Uncontrolled infection, bleeding or hemodynamic instability
- Small liver size (by imaging)
- Chronic dialysis

Summary of Analysis Populations



Overall Study Outcomes

Primary Endpoint: Overall Survival
ITT Population with minimum follow-up of 91 days



Secondary Endpoint: Proportion of Survivors
ITT Population at d28 and d91

	ELAD (%)	Control (%)	p-value (Pearson's chi-squared)
28 days	76.0	80.4	0.46
91 days	59.4	61.7	0.74

Safety: Treatment Emergent Serious Adverse Events (TESAE)

	ELAD (%) (n=95)	Control (%) (n=108)
Subjects Reporting at Least One TESAE (>5% of ELAD Treated Subjects)	76.8	69.4
TESAE Preferred Term		
Hepatic Failure	13.7	9.3
Anemia	8.4	5.6
GI Hemorrhage	7.4	5.6
Multi-organ failure	7.4	9.3
Ascites	6.3	12
Hepatic Encephalopathy	6.3	3.7
Acute Renal Failure	6.3	11.1
Deaths (through 91 days)	39	41
Deaths attributed to ELAD	2	-

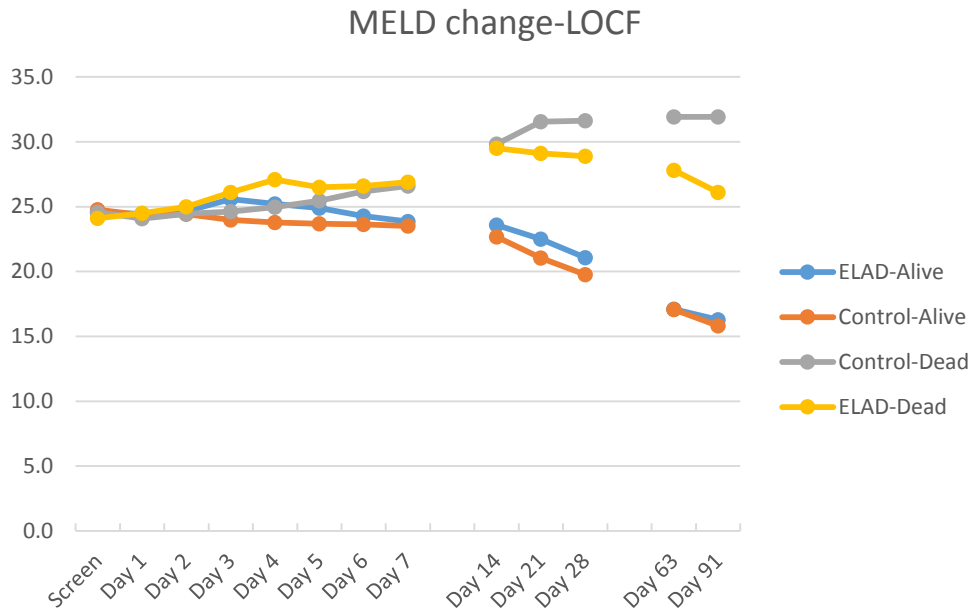
Non-serious adverse events were balanced except for:

- anemia (48% vs. 18%)
- thrombocytopenia (37% vs. 11%)
- coagulopathy (33% vs. 12%)
- hypotension (33% vs. 18%)

Pre-specified Analysis of VTI-208 Data Suggested Significant Impact of Baseline MELD on 91d Survival

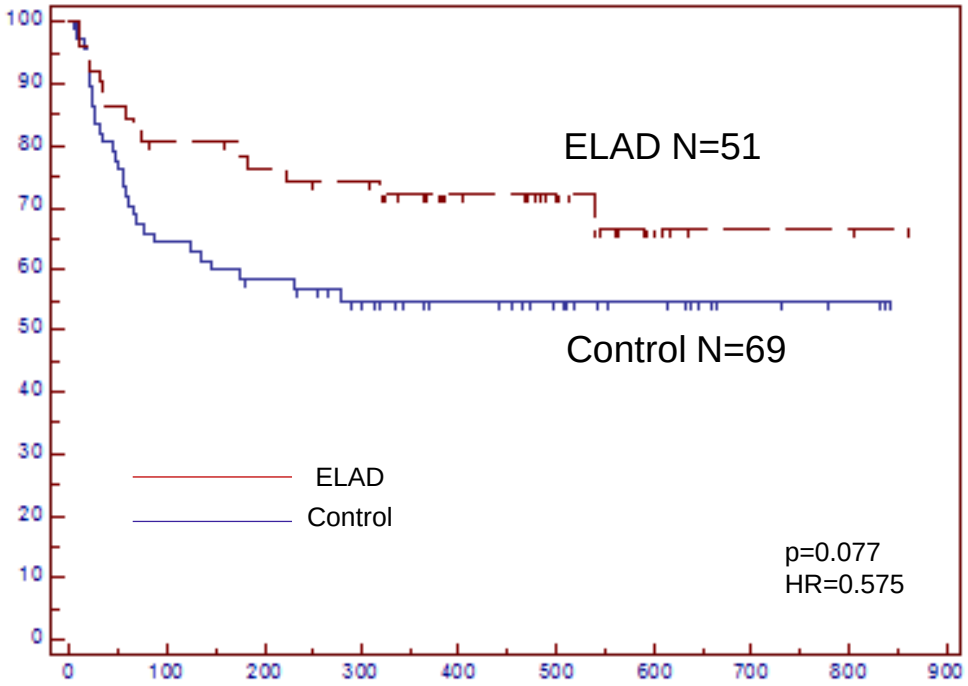
- Significant differences in outcome between low and high MELD groups (p=0.0001)
- Trend towards improved survival in ELAD vs Control for MELD <28 (p=0.07) and reduced survival for MELD >28 (p=0.07)
- MELD stabilization at d7 is predictive of outcome in MELD <28 subgroup

VTI-208 Alcohol-Induced Liver Decompensation (US, Europe, Australia)									
Baseline Parameter	Total	Dead	Alive	Chi-square p value		Total	Dead	Alive	Chi-square p value
MELD <28	120	28.3%	71.7%	0.0001	ELAD	51	19.6%	80.4%	0.07
					Control	69	34.8%	65.2%	
MELD ≥28	83	55.4%	44.6%		ELAD	45	64.4%	35.6%	0.07
					Control	38	44.7%	55.3%	

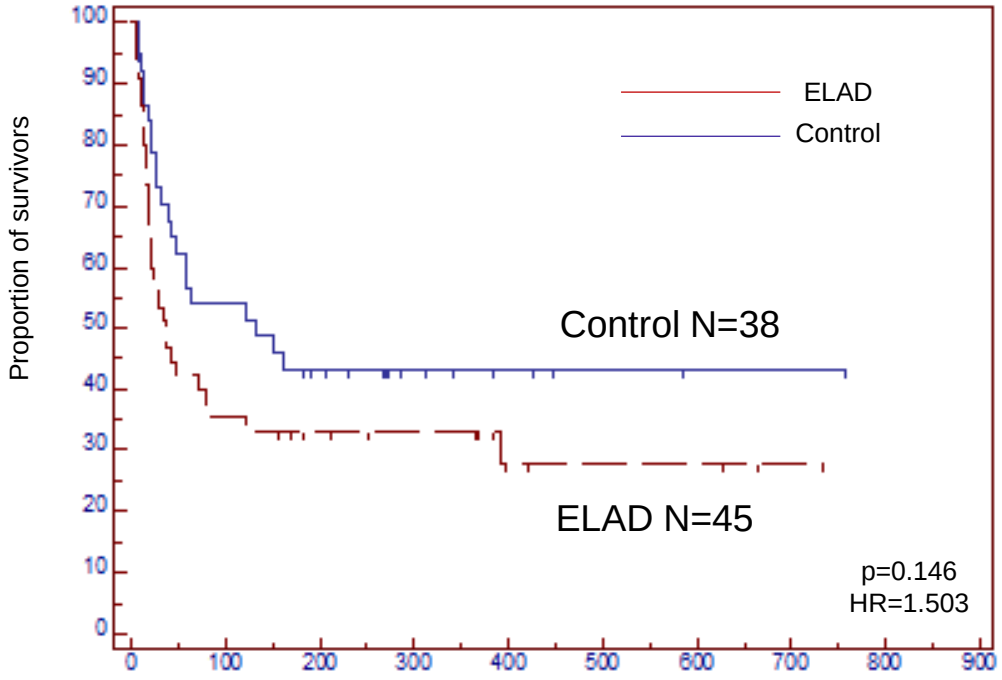


VTI-208 Survival Curves for Pre-Specified Subgroup Analysis Confirms MELD-dependent ELAD Response in VTI-208

120 patients ITT with MELD <28



83 patients ITT with MELD ≥28



Note: Baseline parameters were balanced between ELAD and Control in both subgroups.

Prior ACLF Data Suggested Significant Impact of Baseline Creatinine on 91d Survival

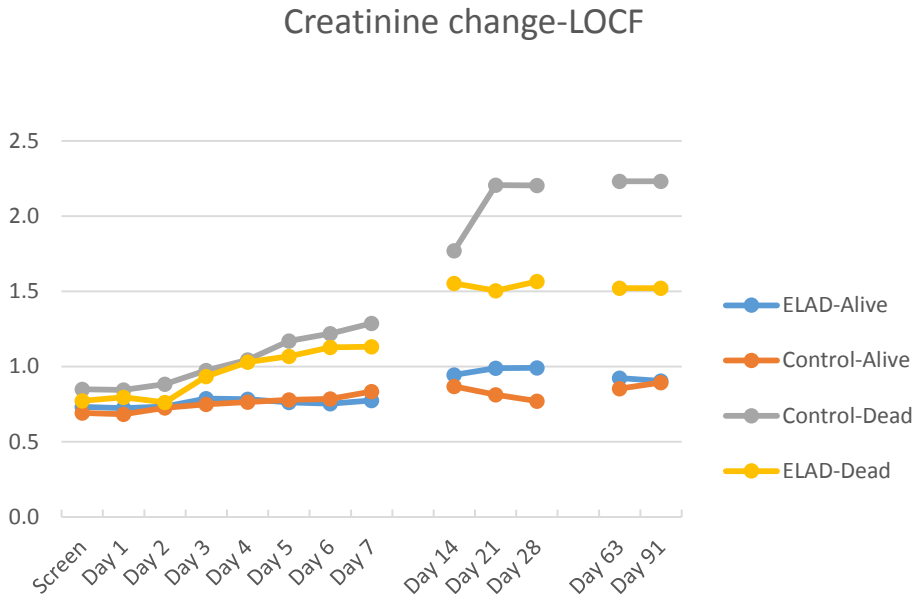
- Proportion of survivors at 91 day showed significant difference between low creatinine group and high creatinine group ($p<0.05$).
- In subjects with Creatinine <1.3mg/dL, 91 day survival revealed ELAD survival of 100% versus control survival of 54.5% ($p<0.05$).
- No difference in survival in high creatinine group

VTI-206 Acute on Chronic Liver Failure (US, Europe)									
Baseline Parameter	Total	Dead	Alive	Chi-square p value		Total	Dead	Alive	Chi-square p value
Creatinine <1.3mg/dL	19	26.3%	73.7%	0.049	ELAD	8	0%	100%	0.03
					Control	11	45.5%	54.5%	
Creatinine ≥1.3mg/dL	31	54.8%	45.2%		ELAD	16	56.2%	43.8%	N.S.
					Control	15	53.3%	46.7%	

Pre-Specified Analysis of VTI-208 Data Suggested Significant Impact of Baseline Creatinine on 91d Survival

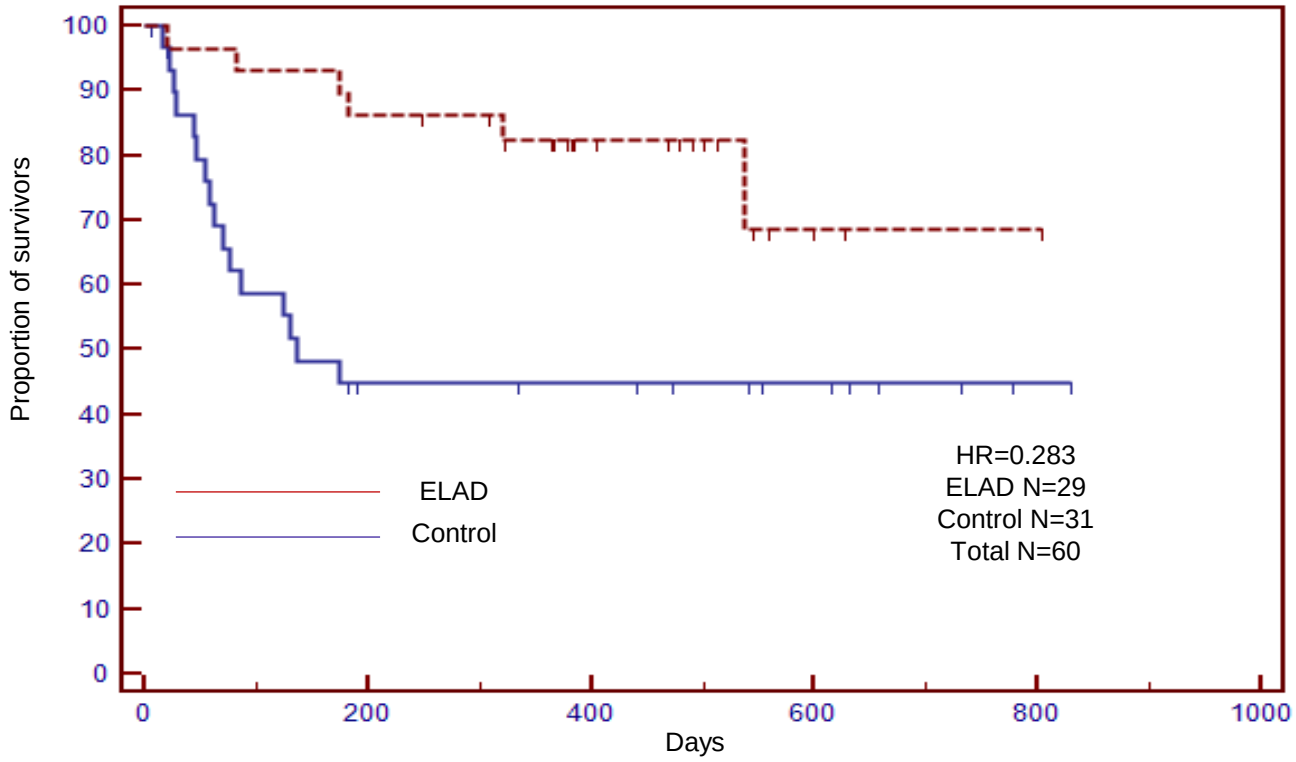
- Significant differences in outcome between low and high baseline creatinine groups (p=0.018)
- No difference in 91d survival in ELAD vs Control for creatinine <1.3mg/dL and trend towards reduced survival in ELAD group for creatinine ≥1.3mg/dL (p=0.15)
- Change in creatinine at d7 is highly predictive of d91 survival in MELD <28 subgroup

VTI-208 Alcohol-Induced Liver Decompensation (US, Europe, Australia)									
Baseline Parameter	Total	Dead	Alive	Chi-square p value		Total	Dead	Alive	Chi-square p value
Creatinine <1.3mg/dL	157	35.0%	65.0%	0.018	ELAD	71	32.4%	67.6%	N.S.
					Control	86	37.2%	62.8%	
Creatinine ≥1.3mg/dL	46	54.3%	45.7%		ELAD	25	64%	36%	0.15
					Control	21	42.9%	57.1%	



Confirmatory Trial Underway (VTL-308)

- Planned for ~40 sites
- US, UK, Germany, Spain
- Enrolment criteria based in pre-specified subgroups of VTI-208
  - Post-hoc analysis revealed HR=0.283 (p<0.001 if pre-specified)
- Age <50, MELD <30, INR ≤2.5, Creatinine <1.3mg/dL, Bilirubin ≥16mg/dL



Transplants in VTI-208/VTI-208E

Group	# transplants	Time to transplant	Mean time to transplant	Baseline MELD <28
ELAD	2	210d, 254d	232d	1 (210d)
Control	4	85d, 90d, 329d, 424d	232d	2 (85d, 329d)

Conclusions

- ELAD treatment failed to meet primary and secondary survival endpoints
- Serious adverse event incidence was similar between groups
  - ELAD treatment arm had more non-serious adverse events of anemia, thrombocytopenia, coagulopathy and hypotension
  - 2 deaths were attributed to ELAD use
- ELAD treatment showed trend towards improved overall survival in lower MELD (<28) subjects
  - Resolution of acute disease process may reduce need for transplant during the first 180 days
- Stabilized MELD and reduced creatinine at d7 was predictive of 91d outcome
- Rate of transplant was low overall (6/203), with fewer transplants in the ELAD group (2/96) than the Control group (4/107)
  - Immature data preclude definitive conclusions
  - Robust extended survival data suggest early treatment prior to the development of secondary organ dysfunction might avoid the need for later transplantation
- A confirmatory clinical trial is underway excluding secondary organ dysfunction at baseline

Multicenter ELAD Study Group

40 Sites Enrolled Subjects

AUSTRALIA
- Flinders Medical Centre, Adelaide
- Sir Charles Gairdner, Perth
- Royal Prince Alfred Hospital, Sydney

UK
- University of Birmingham, Queen Elizabeth Hospital, Birmingham
- Royal Free Hospital, London
- Cambridge University Hospital, Cambridge
- Royal Infirmary, Edinburgh
- Kings College Hospital, London

UNITED STATES
- Albert Einstein Medical Center, Philadelphia, PA
- Baylor University Medical Center, Dallas, TX
- Beth Israel, Boston, MA
- Capital Health Medical Center, Trenton, NJ
- Cedars Sinai, Los Angeles, CA
- Cleveland Clinic, Cleveland, OH
- Cleveland Clinic Florida, Weston, FL
- Columbia University Medical Center, New York, NY
- Drexel University, Philadelphia, PA
- East Carolina University, Greenville, NC
- Emory University, Atlanta, GA
- Georgetown University, Washington DC
- Maricopa Medical Center, Phoenix, AZ
- Methodist Dallas Medical Center, Dallas, TX
- Montefiore Medical Center, New York, NY
- New York University, New York, NY
- North Shore University Hospital, Manhasset, NY
- Piedmont Atlanta Hospital, Atlanta, GA
- Rush University Medical Center, Chicago, IL
- Rutgers University, Newark, NJ
- Southern California GI Liver Centers, San Diego, CA
- Swedish Medical Center, Seattle, WA
- Tampa General Hospital, Tampa, FL
- University of Mississippi, Jackson, MS
- University of Arizona, Tucson, AZ
- University of Arkansas, Little Rock, AR
- University of California at San Diego, San Diego, CA
- University of Minnesota, Minneapolis, MN
- University of Pittsburgh Medical Center, Pittsburgh, PA
- University of Southern California, Los Angeles, CA
- University of Washington, Seattle, WA
- Westchester Medical Center, Westchester, NY