Early Change in Bilirubin Level (ECBL) as a Surrogate for Outcome in ELAD Clinical Study of Severe Alcoholic Hepatitis (sAH)

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Disclosures

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Background

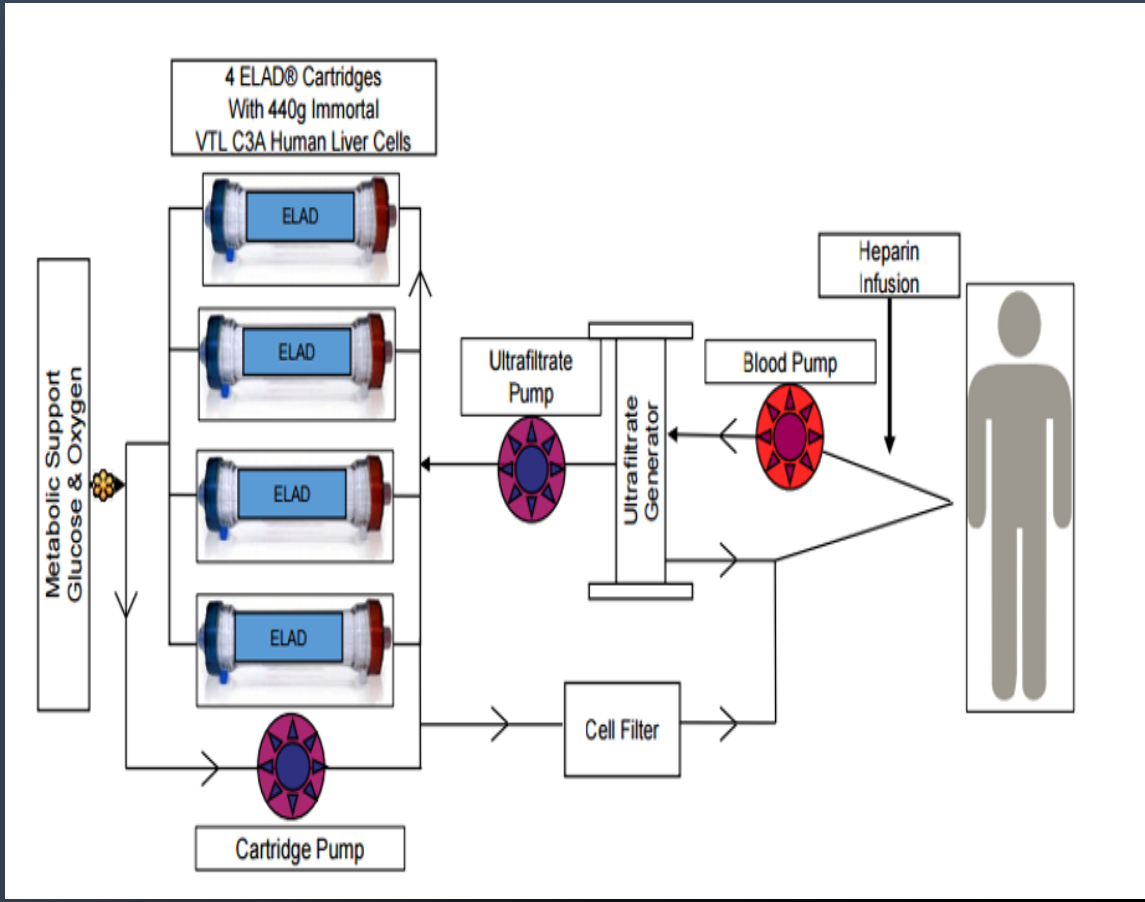
- Alcoholic Hepatitis (AH) is an inflammatory disease, characterized by cell injury, oxidative stress, cell death and impaired regeneration
- Elevated bilirubin is one of the critical diagnostic features of AH
- Changes in serum bilirubin predict outcome in sAH

Prognostic Scoring Algorithms in AH

Name	Baseline bilirubin	ECBL	INR/PT	Creatinine	Age	Urea	Albumin	WBC
MDF	X		X					
GAHS	X		X		X	X		X
MELD	X		X	X				
ABIC	X		X	X	X			
ECBL	X	X						
Lille	X	X	X	X	X		X	

ECBL: Early Change in Bilirubin Levels, MDF: Maddrey Discriminant Function, MELD: Model for End-Stage Liver Disease, GAHS: Glasgow Alcoholic Hepatitis Score, ABIC: Age, Bilirubin, INR, Creatinine, Lille: The Lille Model

The ELAD System



C3A Cells Express Numerous Proteins Relevant to Liver Function

- Anti-inflammatory proteins[1]
  - IL-1 receptor antagonist
  - Alpha-1-antitrypsin
  - Gelsolin • Growth factors
- 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]
  - CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5

- [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 Trial

Design

- International, prospective, randomized, controlled, open-label Phase III trial
- 200 subjects
- 1:1 randomization:

◊ ELAD (5 days continuous therapy) plus standard of care (SOC) or

◊ SOC alone

- Primary endpoint:

  Kaplan-Meier analysis of overall survival

- Secondary endpoints:

  Proportion of survivors at 28 and 91 days

Inclusion

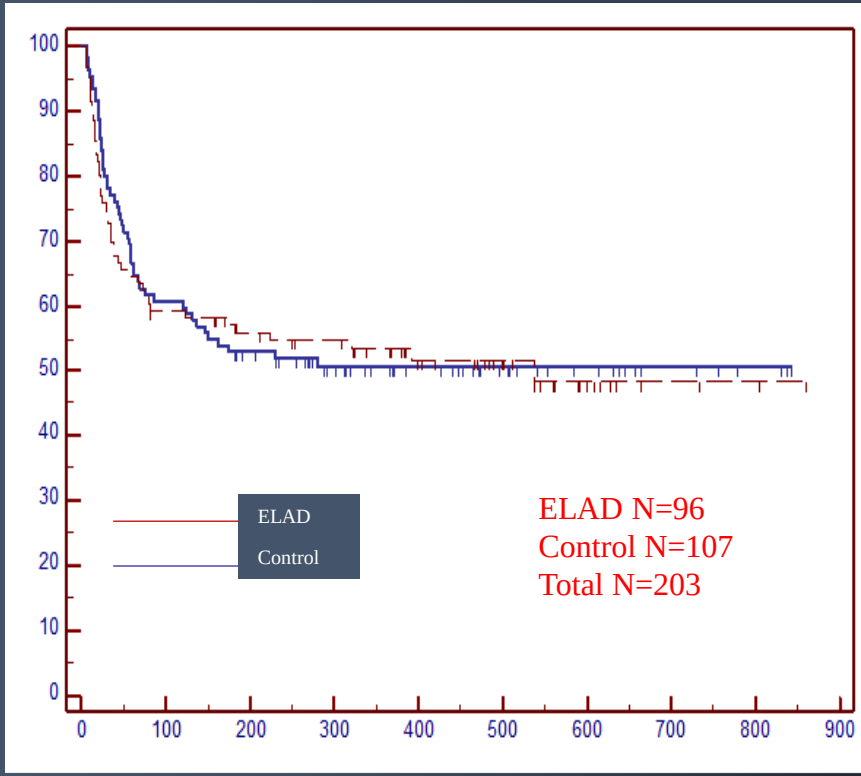
- Age >18
- Total bilirubin ≥8 mg/dL
- EtOH within 6 weeks of onset of symptoms

Exclusion

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

ITT Analysis of Study Endpoints

ITT Population : 96 ELAD, 107 Control



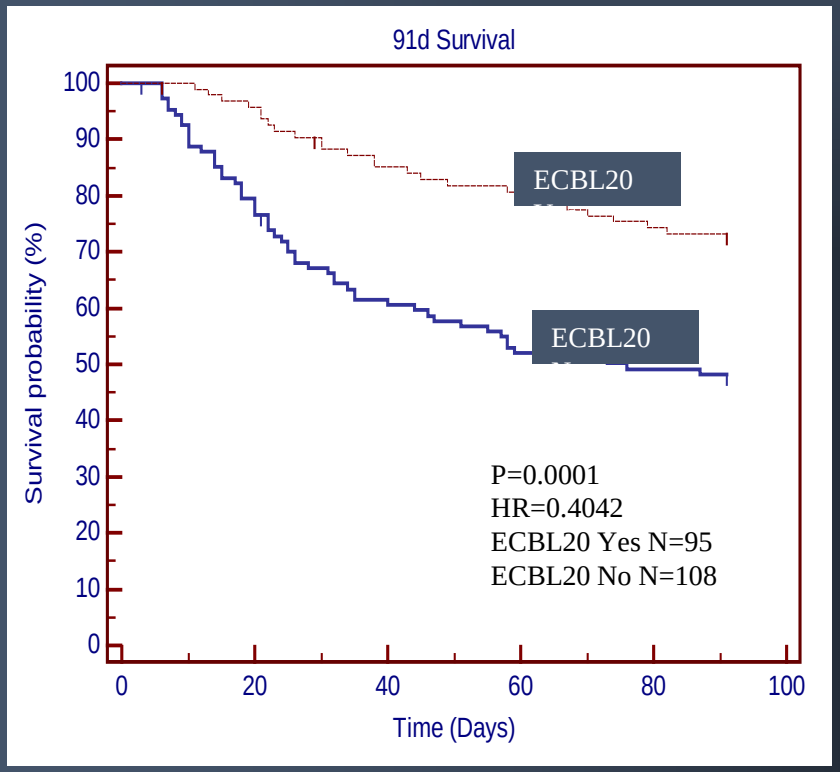
Secondary Endpoints: Proportion of Survivors			
	ELAD (%)	Control (%)	p-value (Pearson's chi-squared)
28 days	76.0	80.4	0.46
91 days	59.4	61.7	0.74

Definition of Early Change in Bilirubin (ECBL)

- ECBL = ΔTBIL from Day1 to Day 7
- ECBL20 Yes = $\geq$20% reduction in TBIL
- ECBL20 No = $\leq$20% reduction in TBIL
- Literature demonstrates that a 20% or greater ECBL results in a significant correlation with survival

Morris et al, 2005; Lee et al, 2014, Li et al, 2016

ECBL20 Predicts Outcome in Study Population Independent of Study Group



N=203	Total	Alive	Dead	% Alive	p-value*
ECBL20 Yes	95	70	25	70/95 (74%)	0.0003
ECBL20 No	108	53	55	53/108 (49%)	

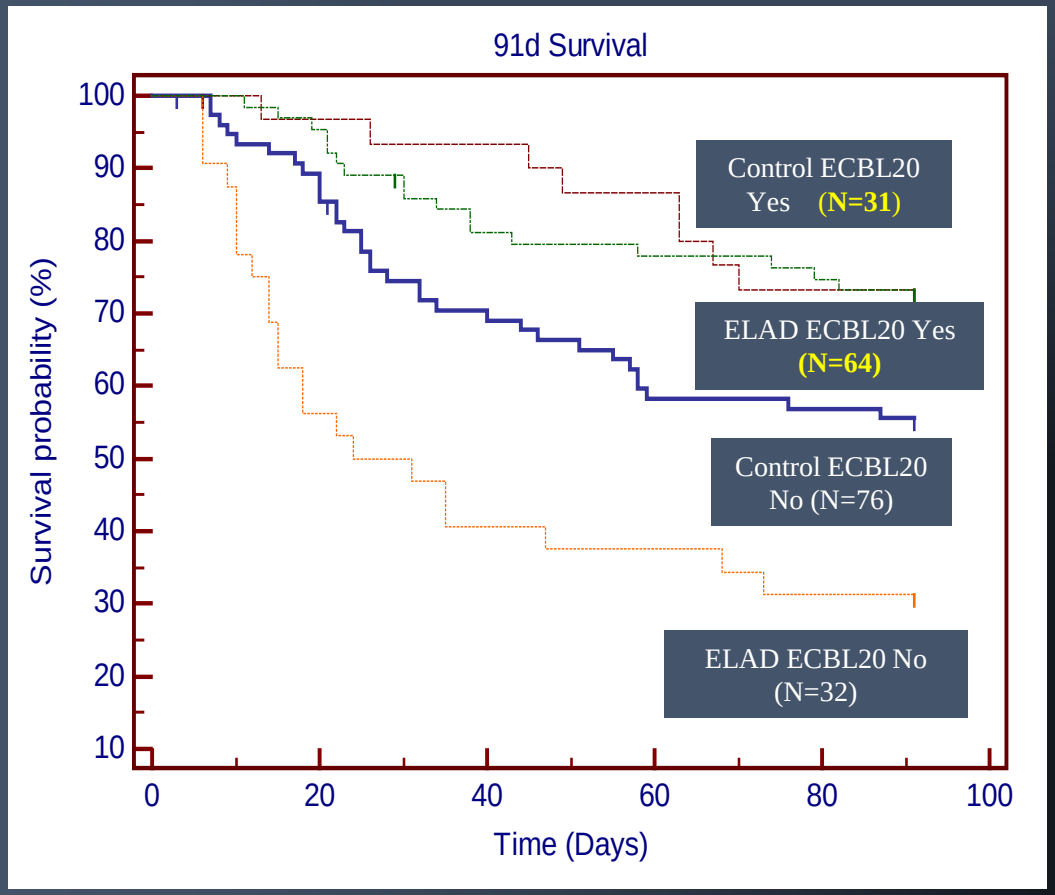
Significantly more 91-day survivors in ECBL20 Yes vs. ECBL20 No ($p<0.01$)

Steroid Use Has No Impact on ECBL20

- Steroid use at screen and during the first 7 days was the same in ECBL20 Yes subjects (32/95, 34%) and ECBL20 No subjects (31/108, 29%)

ITT Population (N=203)	Total # of Subjects	Steroid Use at Screen and during the first 7 days
ECBL20 Yes	95	32/95 (34%)
ECBL20 No	108	31/108 (29%)
Chi-square p-value (ELAD vs Control)		N.S.

ELAD use Results in More Frequent ECBL20



- Twice as many subjects had ECBL20 Yes in the ELAD group than the Control group ($p<0.0001$)
- The survival of ECBL20 No subjects was lower in the ELAD group than the Control group
- Cr≥1.5 and/or INR≥2.5 disproportionately impacts ELAD non-responders

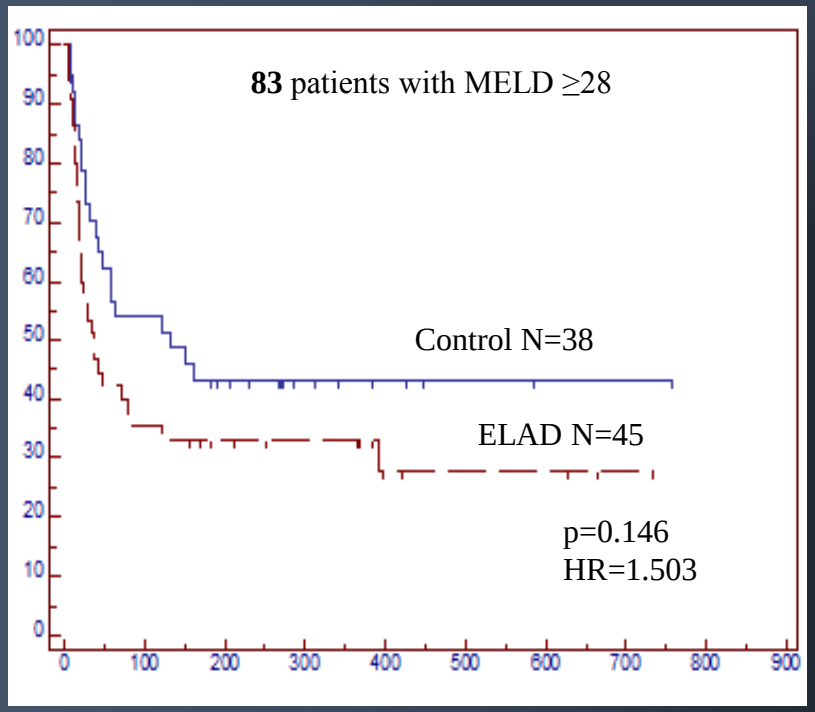
Role of Renal Dysfunction and Coagulopathy on Survival

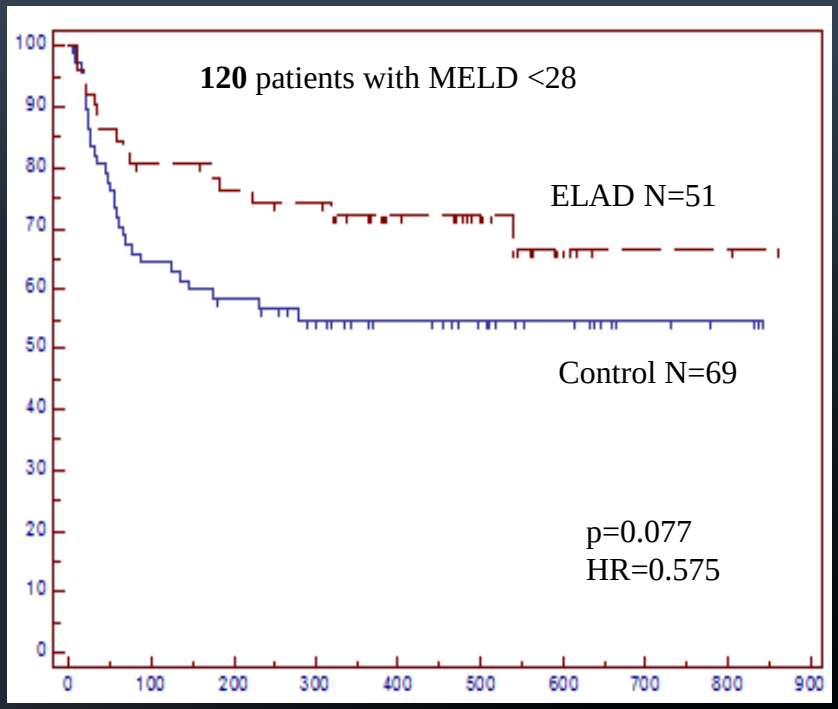
Baseline Parameter	# Subjects	Overall Survival / LTFU: ITT Population		p-value (ELAD vs Control)
		ELAD Treated	Control	
Creatinine ≥1.5mg/dL	**33**	**27.8%**	**53.3%**	**p=0.077**
Creatinine <1.5mg/dL	169	57.1%	52.2%	N.S.
INR >2.5	**36**	**25.0%**	**60.0%**	**p<0.05**
INR ≤2.5	167	57.5%	50.6%	N.S.
Bilirubin ≥25.7mg/dL	102	44.0%	44.2%	N.S.
Bilirubin <25.7mg/dL	101	60.9%	60.0%	N.S.

- MELD: 3.78×ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57×ln[serum creatinine (mg/dL)] + 6.43
- Moreau et al confirms that subjects with creatinine ≥1.5mg/dL and/or INR ≥2.5 are at a higher risk of short term mortality than those without secondary organ dysfunction (Moreau et al. Gastroenterology 2013;144:1426–1437)

Pre-Specified Subgroup Analysis: Effect of MELD

Pre-specified subgroup analysis reveals MELD-dependent ELAD response

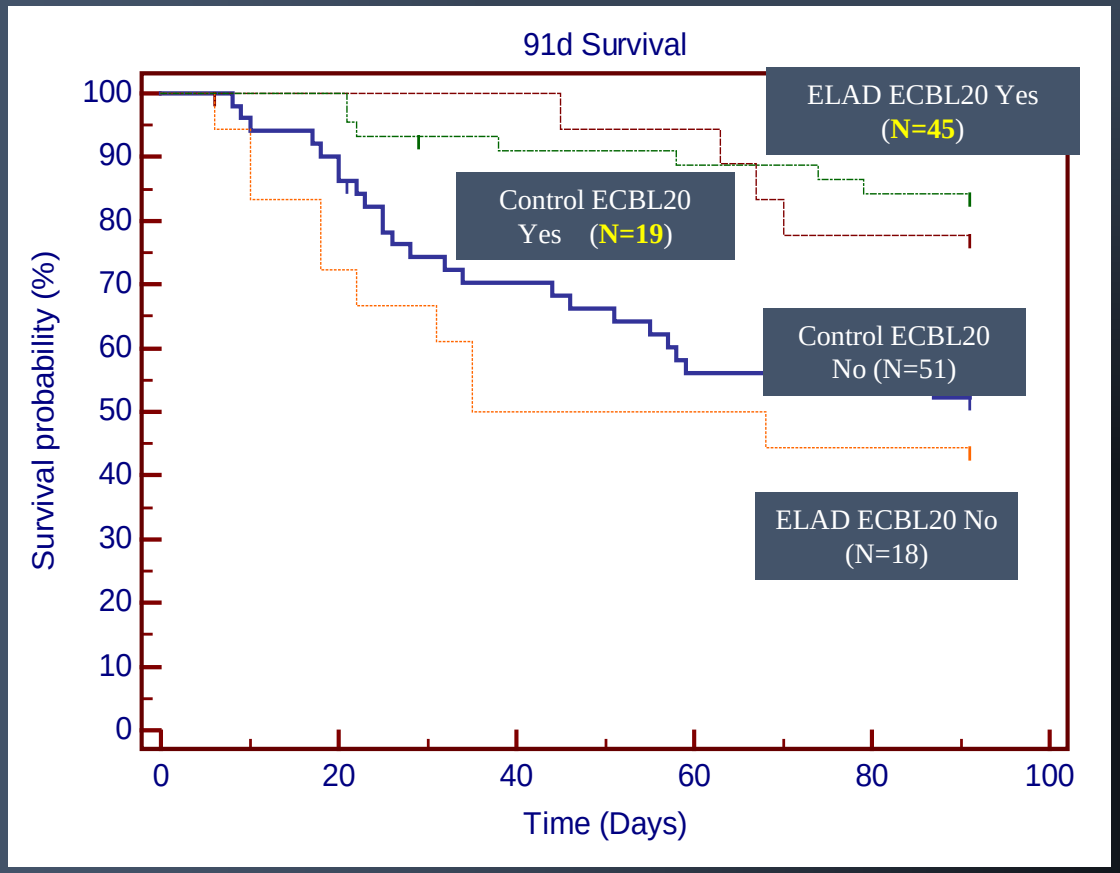




Baseline parameters were balanced between ELAD and Control in both subgroups.

Excluding Patients with Renal Dysfunction and Severe Coagulopathy

Survival according to ECBL

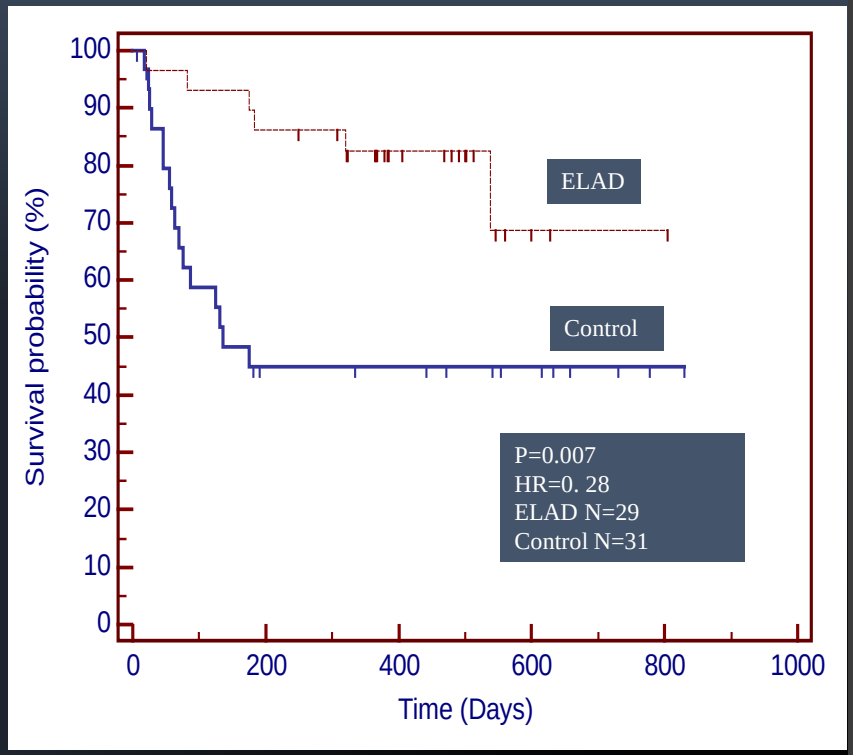


- Excluding patients with Cr ≥1.5 and/or patients with INR ≥2.5
- Survival of ECBL20 Yes subjects was superior to ECBL20 No ($p<0.0001$)
- The survival of ECBL20 No subjects was similar between ELAD and Control group.

ECBL20 - 91-Day Survival- by treatment group (Creatinine<1.5 and/or INR<2.5 Population)

To Confirm these Observations: A New Trial: VTL-308 is Underway

- Potential ELAD benefit observed in post-hoc analysis N=60 in VTI-208
- Enrollment criteria based on pre-specified subgroups of VTI-208
- Age<50, INR≤2.5, Creatinine<1.3 mg/dL, Bilirubin≥16mg/dL, MELD<30
  - Hazard ratio=0.28
  - Nominal p-value = 0.007
- Multinational study: 50 sites
- US, UK, Germany, Austria and Spain



VTI-208

Conclusions

- **ECBL20** is a suitable surrogate endpoint to predict survival
- ECBL20 predicts survival in both ELAD and Control groups
- **In VTI-208** :Significantly more subjects achieve ECBL20 in the ELAD group
- In ELAD treated subjects with Cr>1.5 and INR > 2.5, ECBL non-response results in poorer outcomes
- Excluding subjects with Cr>1.5 and INR >2.5 eliminates this difference
- **VTL-308**: A phase 3 clinical trial is underway to confirm these findings