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and the ELAD Development Team**

**Efficacy and Safety of Human Cell-based Biological Liver Support
System (ELAD[®]) in Subjects with Acute Alcoholic Hepatitis (AAH)
or Acute Decompensation of Cirrhosis (Non-AAH)**

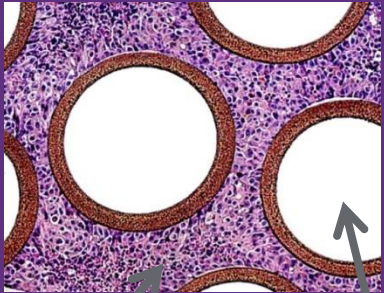
**I have no financial relationships to disclose within the past
12 months relevant to my presentation**

MAY 17, 2012

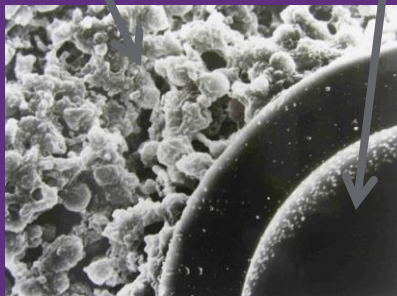
Background

- **Acute on Chronic Liver Failure has limited treatment options:**
 - Corticosteroids, cimetidine, hyperimmune gamma-globulin, exchange transfusions do not affect course of acute hepatitis
 - **AAH patients are usually not eligible for transplant**; have marginal therapies, Corticosteroids and Pentoxifylline, but limited cirrhosis may enable recovery and regeneration of normal liver
- **ELAD is designed to provide continuous support to possibly allow time for native liver to regenerate or provide a bridge to transplantation**

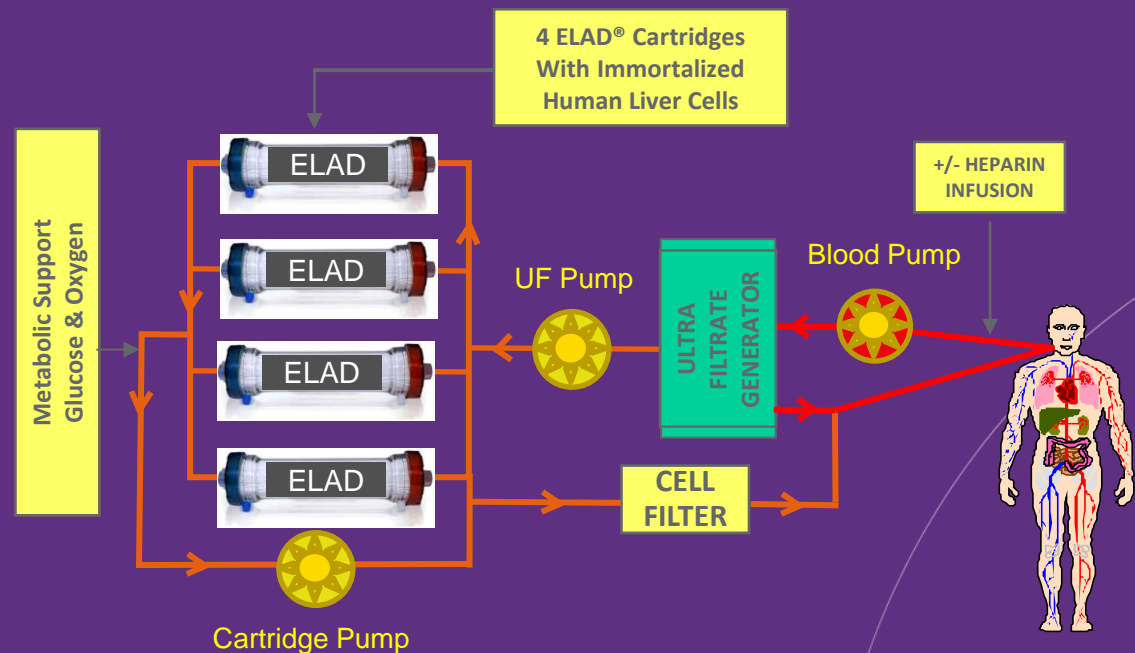
ELAD[®]: Bioartificial Liver Support System



Live human liver cell line
Hollow fiber of bioreactor



- **Allogeneic cellular therapy**
 - 440g of immortalized human C3A liver cells
 - Localized in 4 hollow fiber bioreactors
- Continuous treatment of plasma ultrafiltrate for up to 5 days
- Extra-corporeal support of liver function



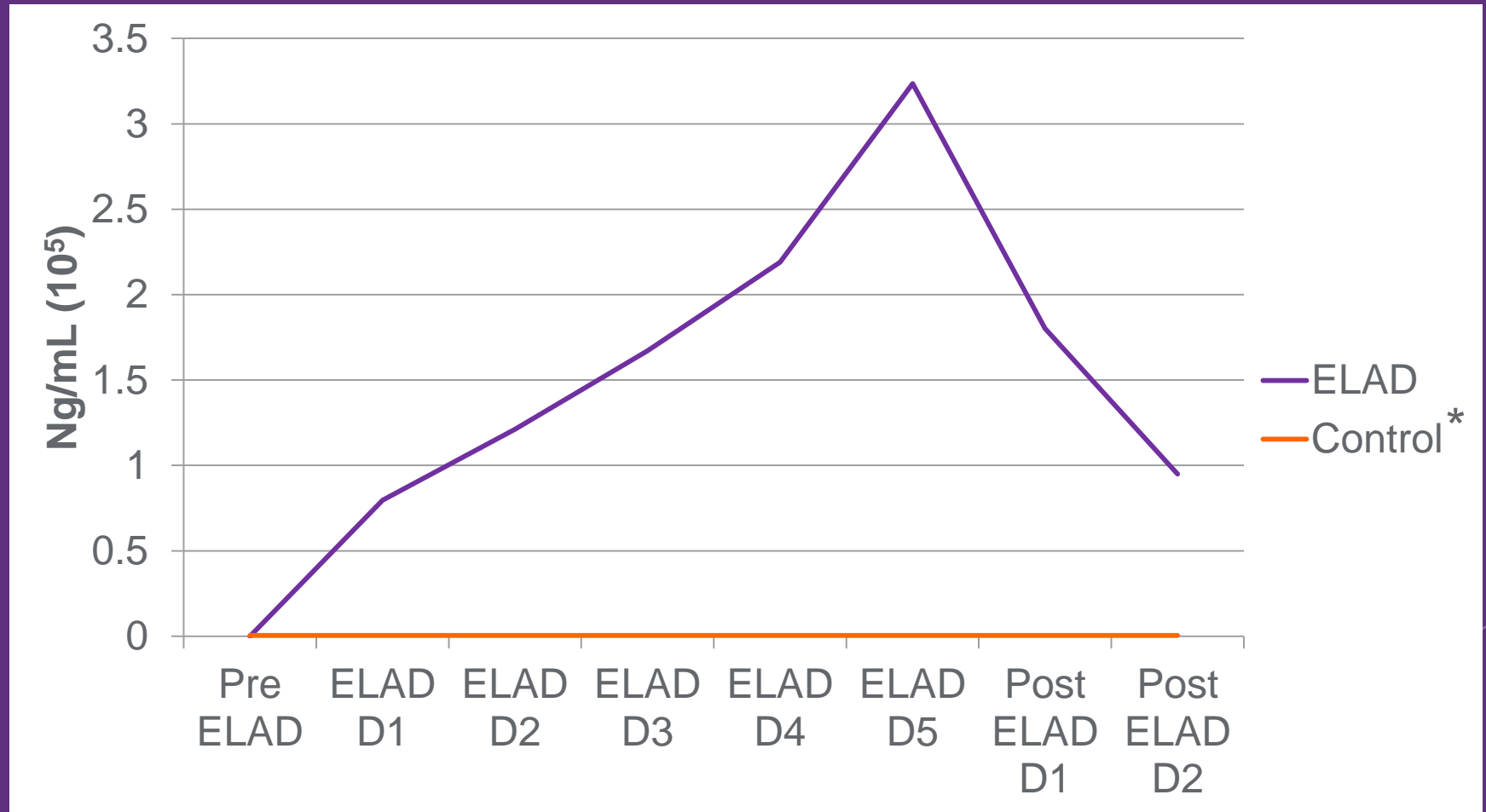
ELAD[®]: Bioartificial Liver Support System



ELAD[®] C3A Cells

- **Allogeneic cell therapy**
 - **Human**: No animal issues
 - **Immortal**: Retain hepatocyte function
 - **Stable**: Can be stored and grown
- **C3A cells retain primary hepatocyte function**
 - Synthesize liver proteins, e.g., albumin, transferrin, factor V
 - Make large quantities of alpha fetoprotein
 - Active P-450 enzyme system
 - Process toxins/metabolites:
 - Consume large amounts of O₂ and glucose
- **With ELAD, rate of plasma flow is 50 mL/min = 3 L/hr = 72 L/day**
 - Higher than plasma exchange therapy (2-3 L/treatment)

AFP levels Treated Subjects VTI-206* (representative values)



*Control levels: <0.005 throughout

*Reference to VTI-206 corrected from VTI-208 post presentation

Trial Design

- **Phase 2b trial in US/EU**
- **Open-label, randomized, controlled**
- **1:1 randomization to ELAD therapy + standard medical therapy (ELAD) - vs - standard medical therapy alone (Control)**

Key Entry Criteria

Inclusion

- 18-67 years old with acute decompensation of chronic liver disease over prior 28 days
- **MELD score 18-35**
- APOCH diagnosis: acute alcoholic hepatitis (AAH) or non-AAH

Exclusion

- **Platelets $<50,000/\text{mm}^3$, INR >3.5**
- **Chronic renal failure**
- Septic shock, major hemorrhage, spontaneous bacterial peritonitis with uncontrolled systemic infection, hemodynamic instability
- Significant concomitant disease
- Previous liver transplant
- DNR

Non-AAH Cohort (n=25)

- **Primary Diagnosis**
 - **Chronic Alcoholic Liver Disease (n=12)**
 - **HCV (n=7)**
 - **Cryptogenic (n=3)**
 - **HAV/HBV (n=1)**
 - **NASH (n=1)**
 - **Autoimmune cholangitis (n=1)**

Efficacy Evaluation

- **Overall survival (OS) at 30 and 90 days**
- Pre-defined analysis populations
 - All subjects, AAH, non-AAH. **AAH / non-AAH** populations were randomized independently. Results presented by subpopulation.
 - Modified intent-to-treat (**MITT**) = subjects who received treatment (baseline failures excluded) with 90-day data
 - **Per-protocol (PP) = subjects who received ≥ 72 hrs treatment (ELAD or control)**
- OS assessed using Kaplan-Meier survival analysis with 2-tail alpha for log-rank test set at 0.05

Study Population

	AAH		Non-AAH		Total	
	ELAD	Control	ELAD	Control	ELAD	Control
Randomized	16	21	13	12	29	33
Baseline failure	0	2	4	0	4	2
Withdrew consent / Lost to follow up	1	3	0	1	1	4
MITT	15	16	9	11	24	27
<72 hrs therapy	2	0	3	1	5	1
PP	13	16	6	10	19	26
Reasons for Baseline Failures:						
Death	0	0	1	0	1	0
Transplant	0	0	1	0	1	0
Ineligible	0	2*	2**	0	2	2
Total	0	2	4	0	4	2

* DNR, portal vein thrombosis

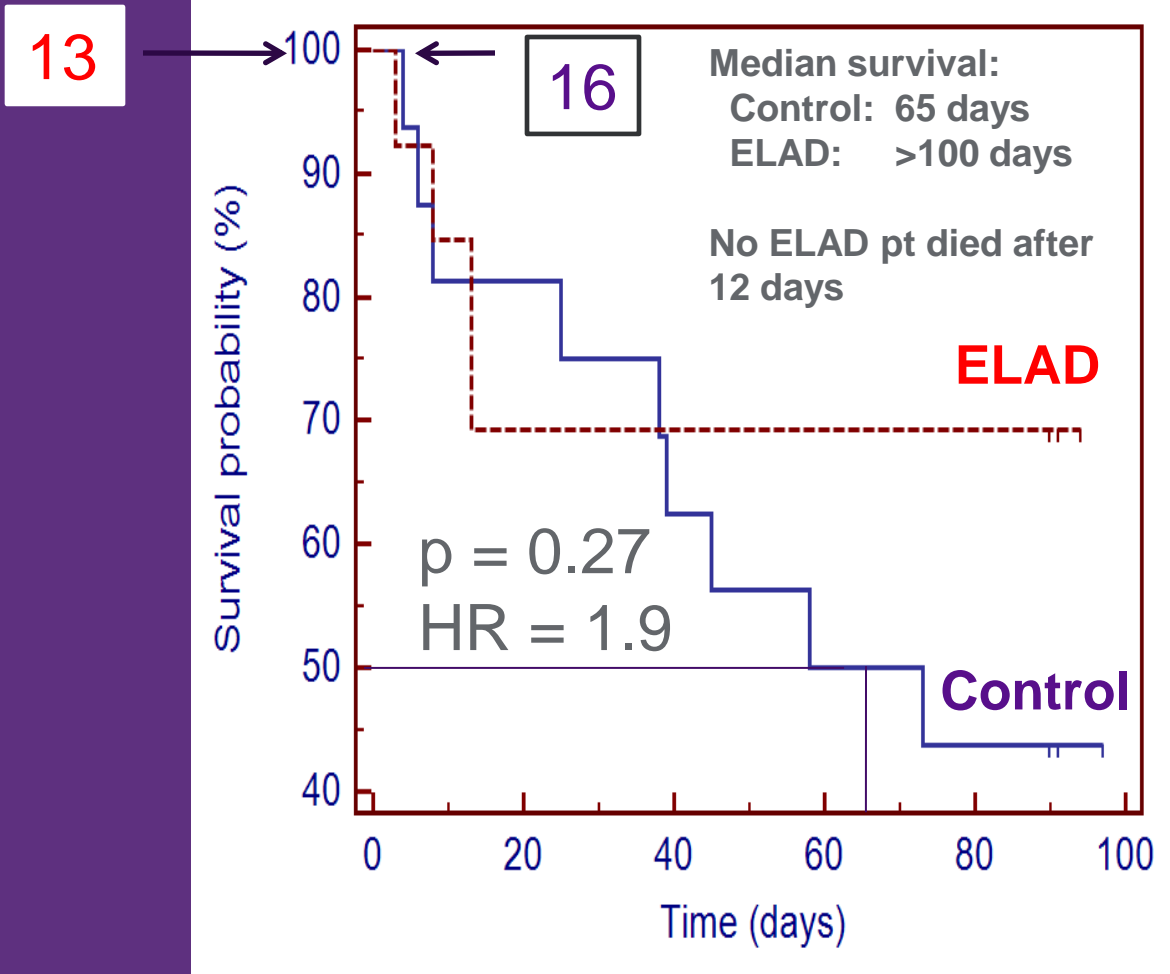
** Hemodynamic instability, systemic fungal infection

Demographics - MITT

	AAH		Non-AAH		Total	
	ELAD n = 15	Control n = 16	ELAD n = 9	Control n = 11	ELAD n = 24	Control n = 27
Males	10 (67%)	8 (50%)	5 (56%)	8 (73%)	15 (63%)	16 (59%)
Caucasian	9 (60%)	15 (94%)	8 (89%)	10 (91%)	17 (71%)	25 (93%)
Black	4 (13%)	0	1 (11%)	0	5 (21%)	0
Age, Mean \pm SD	46.4 \pm 9.2	49.8 \pm 10.3	55.6 \pm 8.9	56.7 \pm 5.6	49.8 \pm 10.0	52.6 \pm 9.2
Baseline MELD, Mean \pm SD	28.4 \pm 5.4	29.3 \pm 5.0	27.1 \pm 5.8	27.5 \pm 4.8)	27.9 \pm 5.5	28.5 \pm 4.9

Mean duration of ELAD treatment (N = 24): 93 hours (range 24 – 144)

Efficacy: AAH Cohort, per-protocol (n=29)



Efficacy: AAH Cohort

	MITT		PP	
	ELAD n = 15	Control n = 16	ELAD n = 13	Control n = 16
OS through Day 90	9 (60%)	7 (43.8%)	9 (69.2%)	7 (43.8%)
Median survival, days	>100	73	>100	65

- **Differences in survival were not statistically significant** ($p > 0.05$) but mathematically favored ELAD
- 1/13 (8%) ELAD-treated and 0/16 Control patients had transplant at 90 days

Efficacy: Non-AAH Cohort

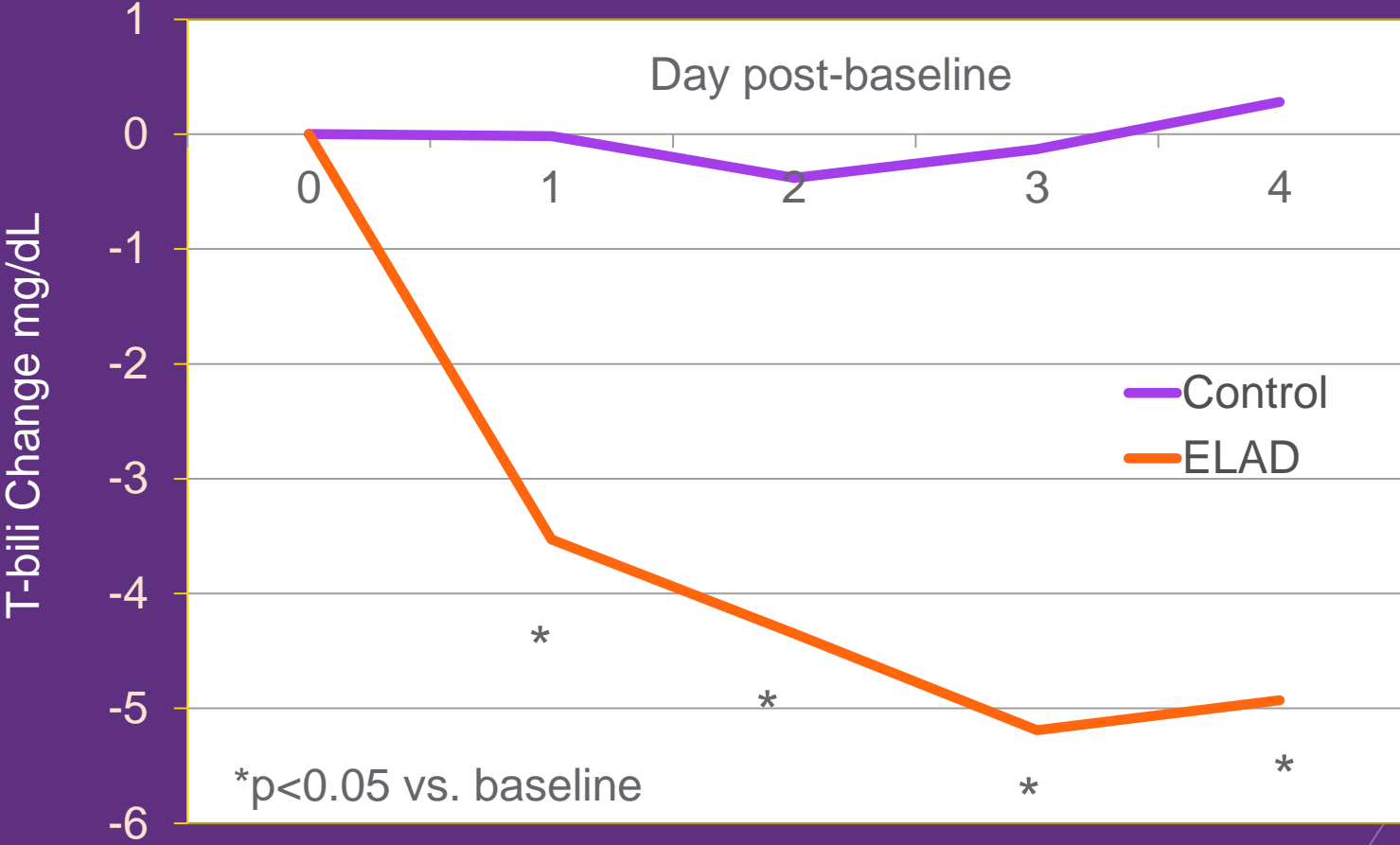
	MITT		PP	
	ELAD n = 9	Control n = 11	ELAD n = 6	Control n = 10
OS through Day 90	2 (22.2%)	6 (54.5%)	1 (17%)	6 (60%)

- **Differences in survival were not statistically significant (p>0.05)**
- 1/6 (17%) ELAD-treated and 4/10 (40%) Control patients had transplant by 90 days

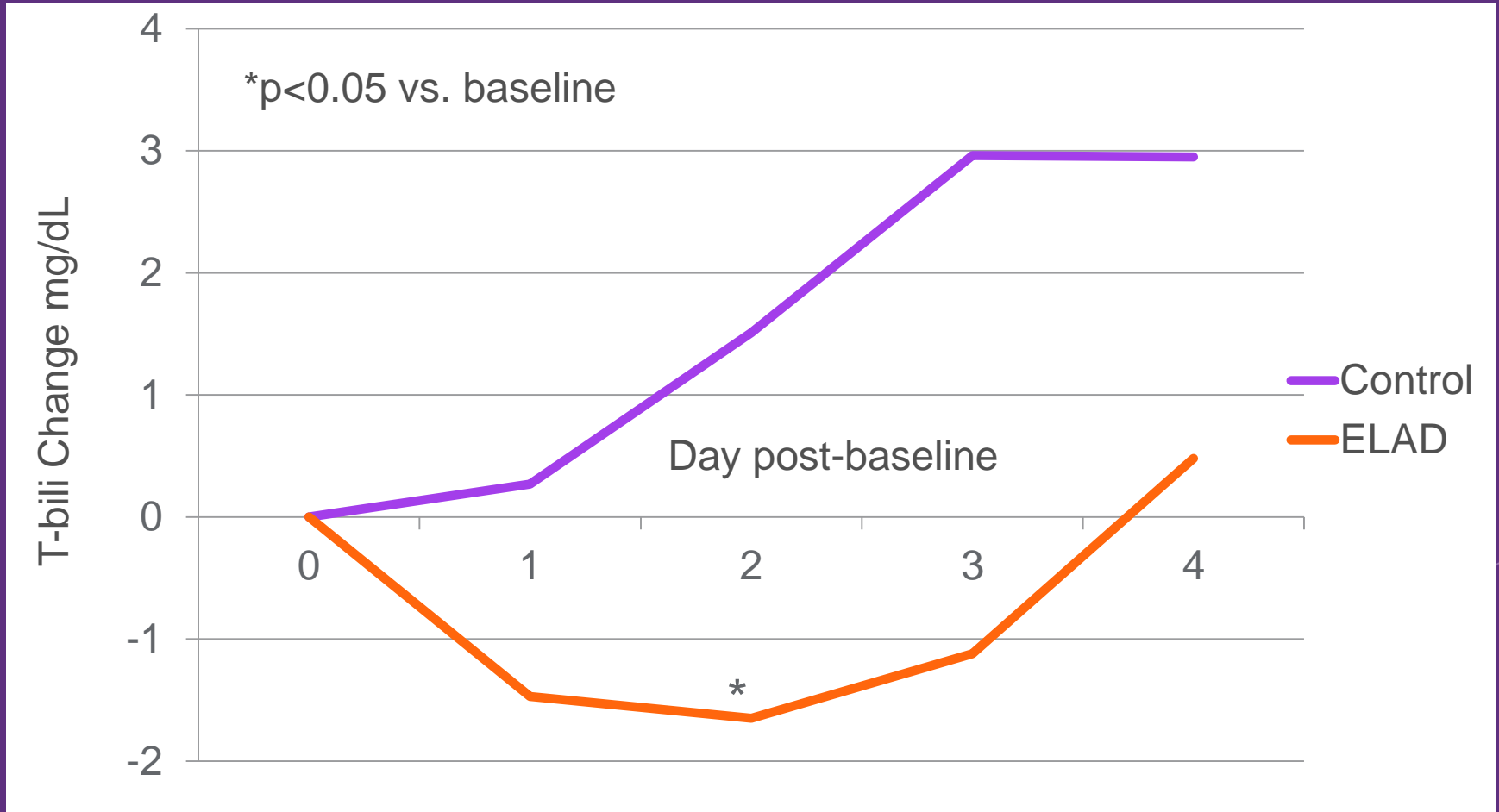
Safety Evaluations

- **Serious adverse events**
 - 28 SAEs reported in 17 ELAD subjects
 - 40 SAEs reported in 20 Control subjects
 - **6 SAEs in 4 ELAD patients reported as possibly related to ELAD:** hematemesis, worsening renal failure, vaginal bleeding, sepsis, GI bleeding, intra-vascular hemolysis

Change in serum t-bilirubin (mg/dL) during treatment AAH Cohort, per-protocol (n=29)



Change in serum t-bilirubin (mg/dL) during treatment Non-AAH Cohort, per-protocol (n=16)



Conclusions

- **No unexpected safety issues**
- **Possible benefit of ELAD for AAH subjects – may provide bridge to recovery and/or transplantation**
- **No benefit observed in AOCH subjects with acute liver failure due to non-AAH disease**
- **Pivotal trials planned for 2012 in AAH and fulminant hepatic failure**

Study Participants

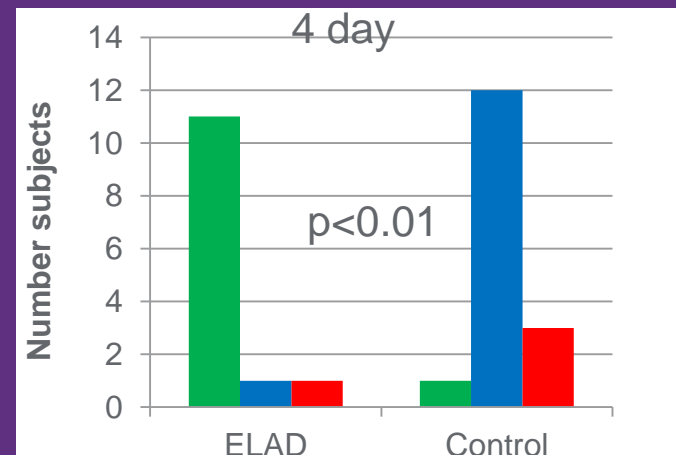
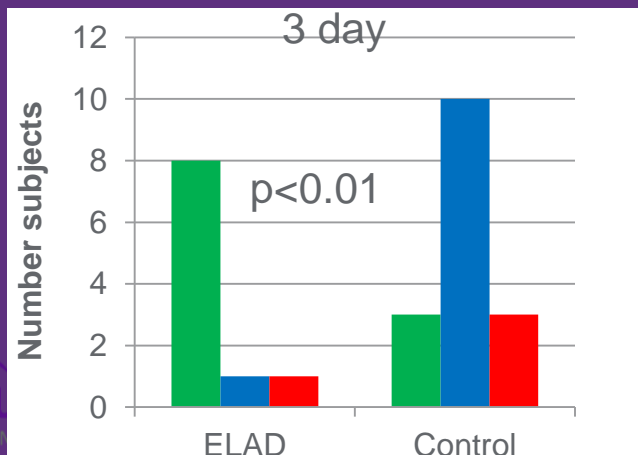
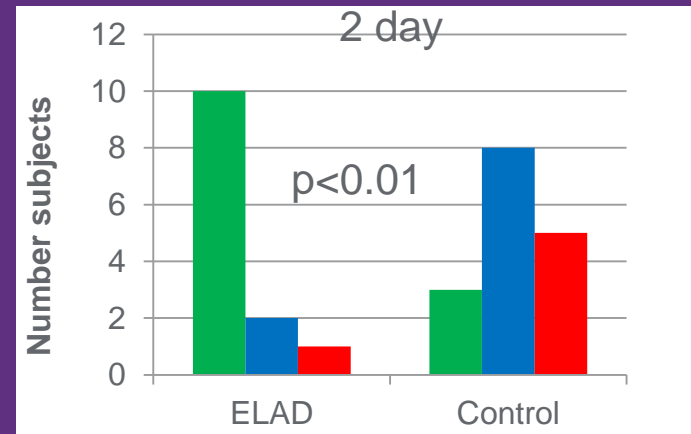
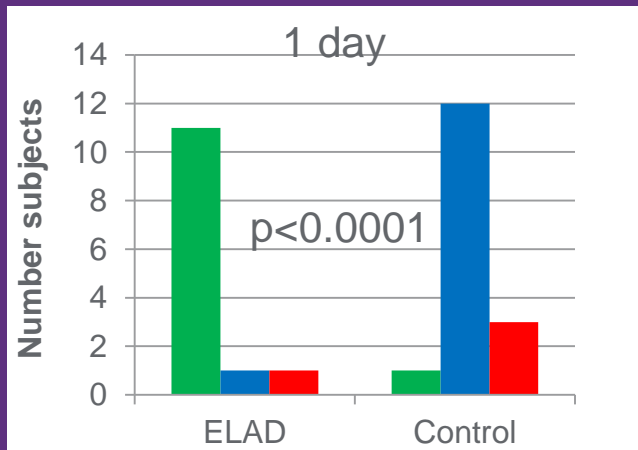
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Subject changes vs baseline in serum bilirubin during ELAD therapy: AAH Cohort, per-protocol (n=29)

- # subjects with > 10% improvement
- # subjects with < 10% change in either direction
- # subjects with > 10% worsening

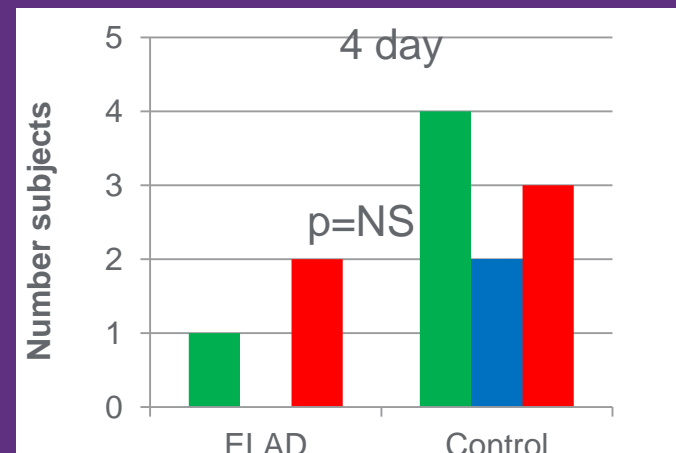
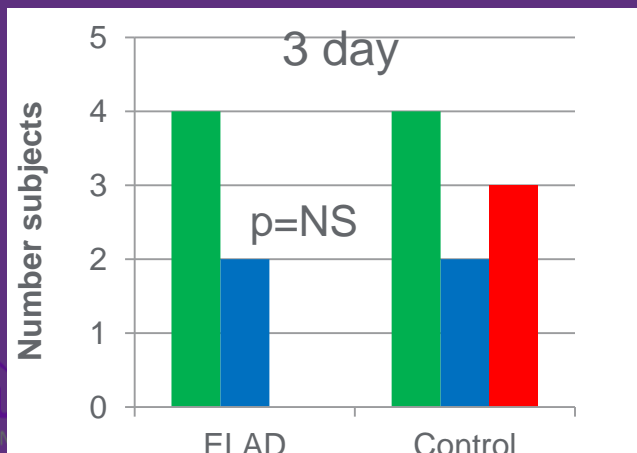
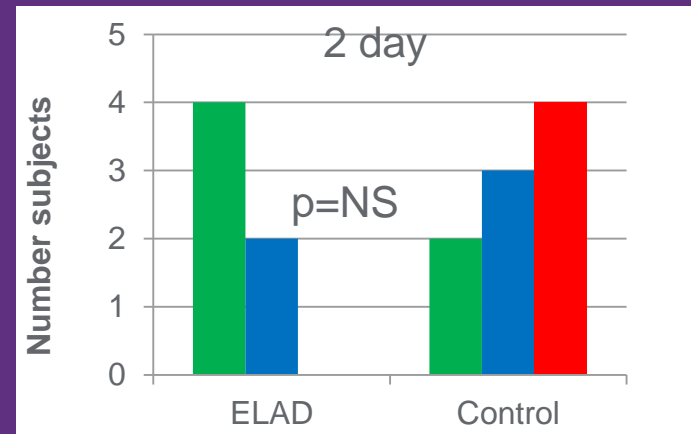
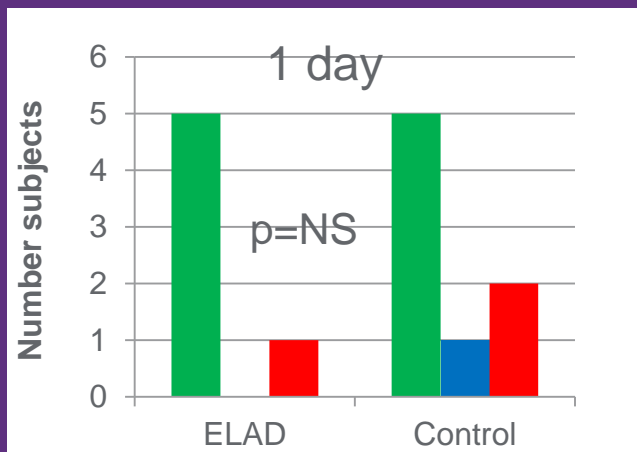
p-values are chi-square vs control



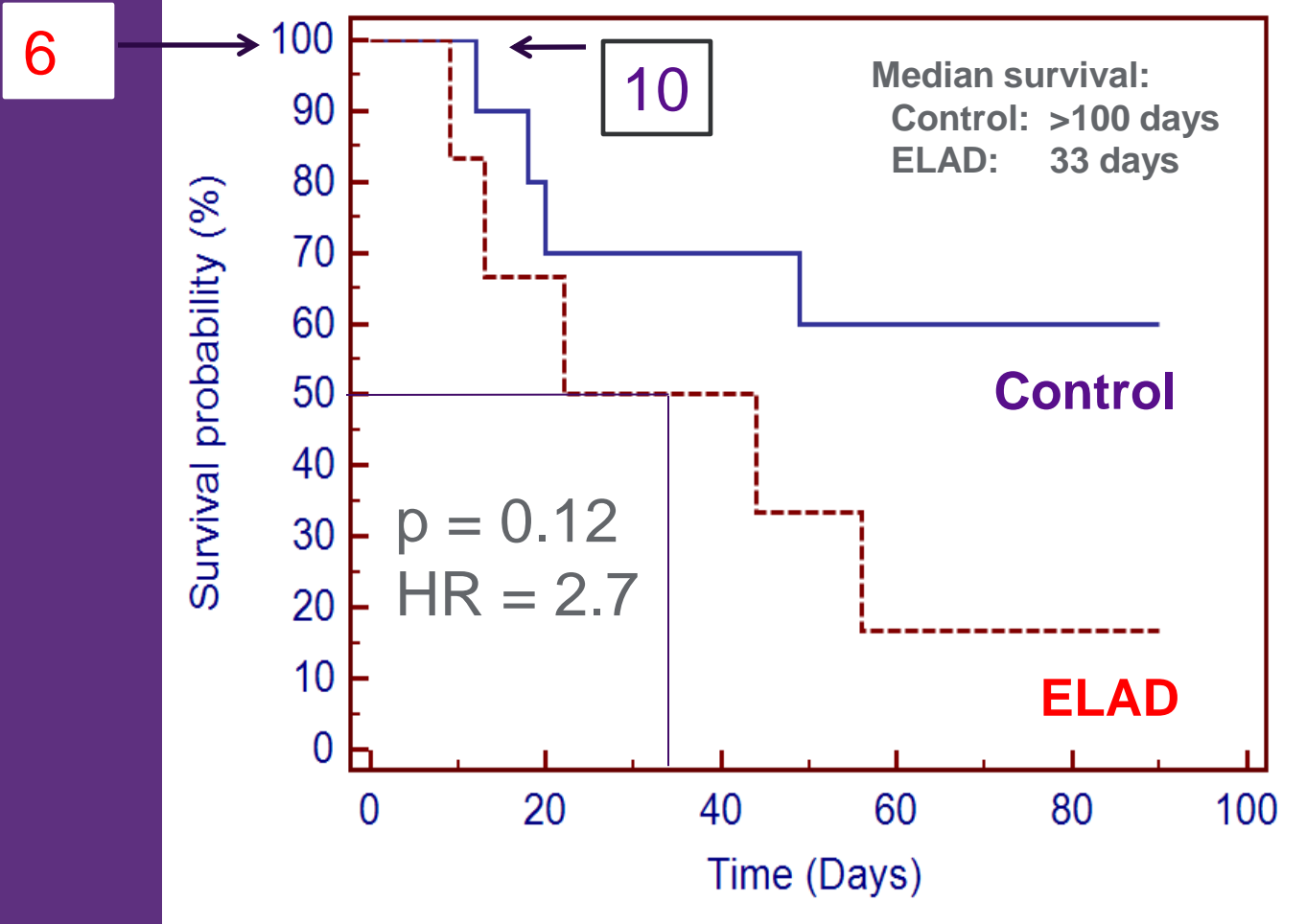
Subject changes vs baseline in serum bilirubin during ELAD therapy: Non-AAH Cohort, per-protocol (n=15)

- # subjects with > 10% improvement
- # subjects with < 10% change in either direction
- # subjects with > 10% worsening

p-values are chi-square vs control



Efficacy: Non-AAH Cohort, per-protocol (n=16)



Albumin Production by Single ELAD[®] Cartridge In-Process Manufacture

