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The Mary Lea Johnson Richards Organ Transplantation Center at NYU 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)

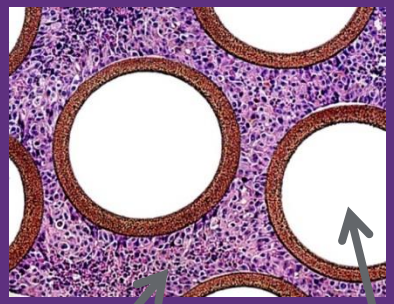
I have no financial relationships to disclose within the past 12 months relevant to my presentation

MAY 17, 2012

Background

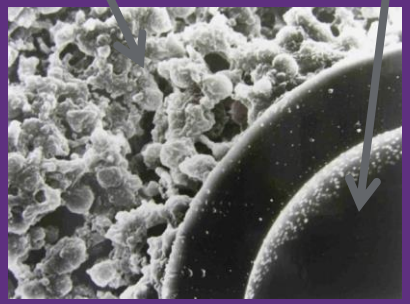
- **Acute on Chronic Liver Failure has limited treatment options:**
  - Corticosteroids, cimetidine, hyperimmune gamma-globulin, exchange transfusions do not affect course of acute hepatitis
  - **AAH patients are usually not eligible for transplant**; have marginal therapies, Corticosteroids and Pentoxifylline, 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

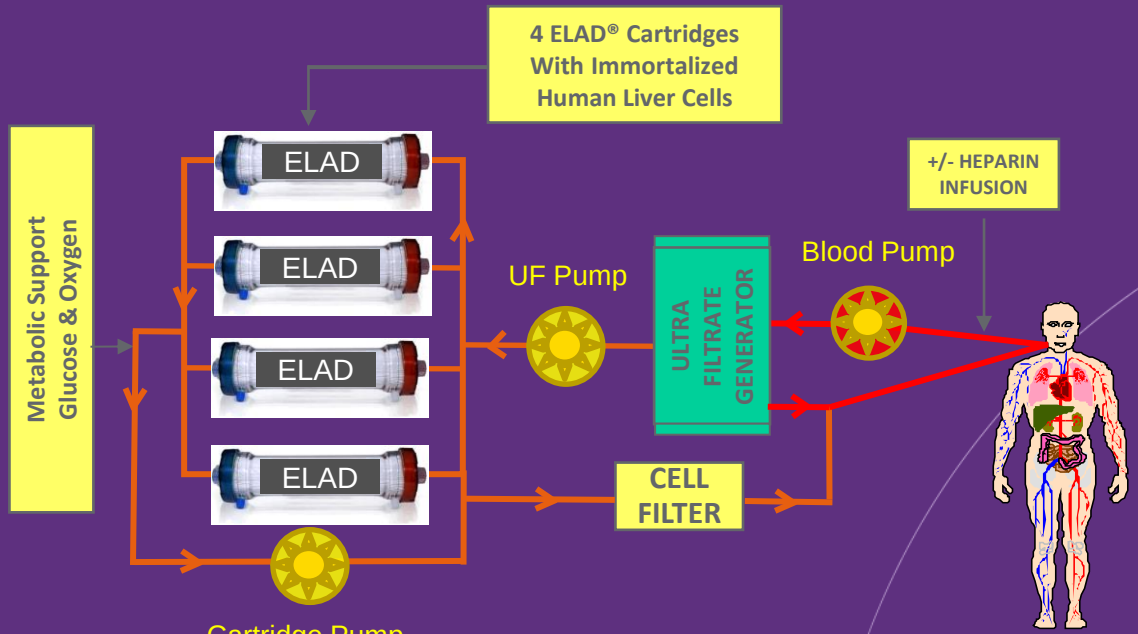


Live human liver cell line

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**



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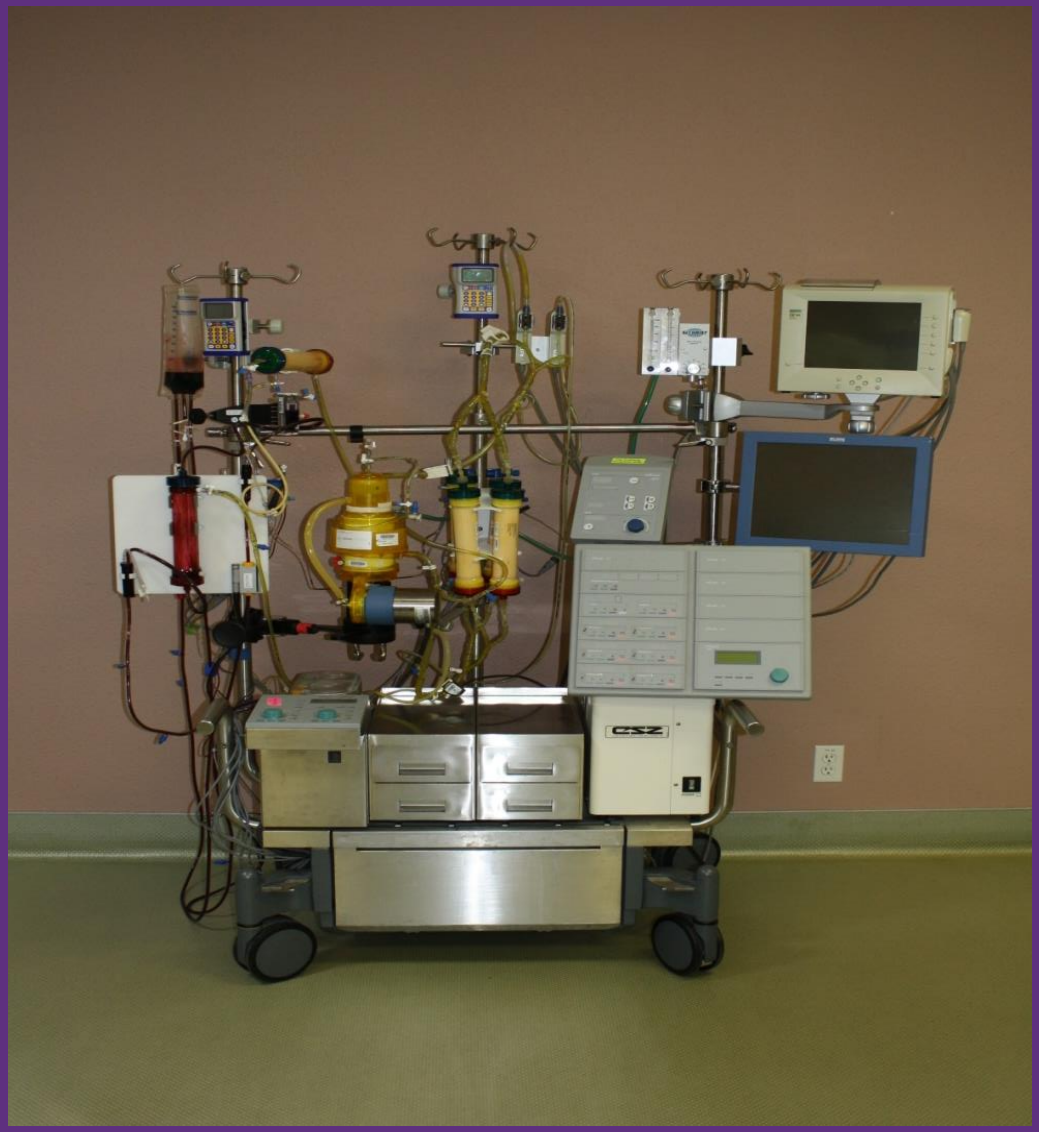
ELAD®: Bioartificial Liver Support System



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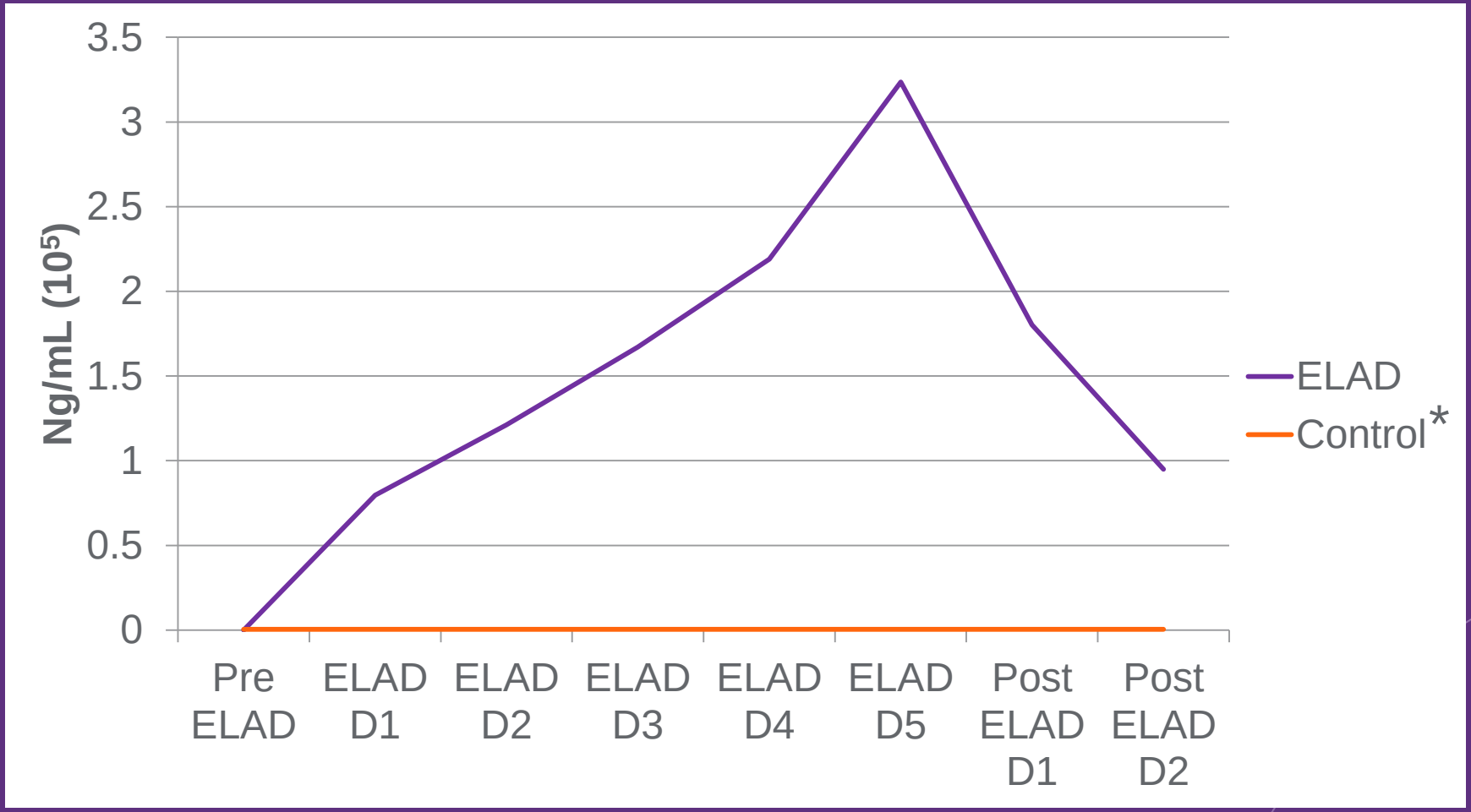
ELAD® C3A Cells

- **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 O_2 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**
- AOCH diagnosis: acute alcoholic hepatitis (AAH) or non-AAH

Exclusion

- **Platelets <50,000/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

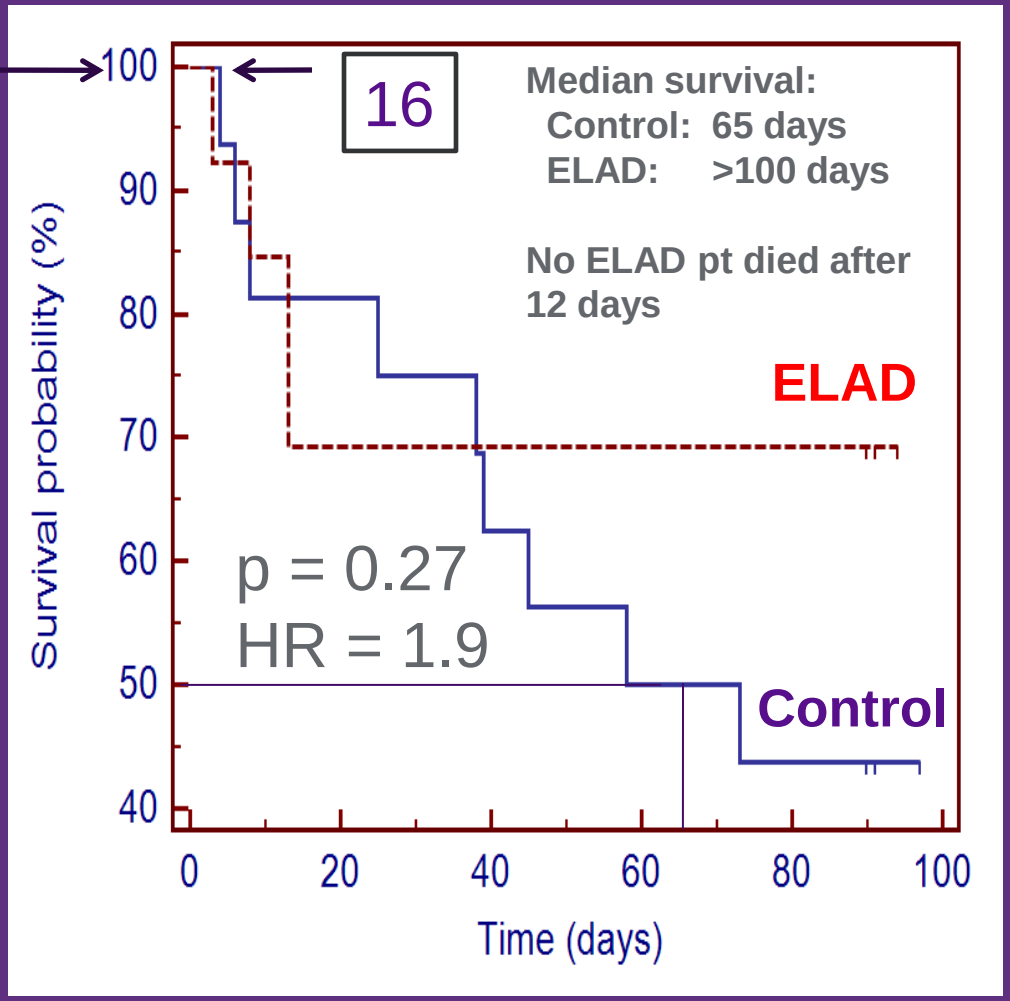
** Hemodynamic instability, systemic fungal infection

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 ± SD	**46.4 ± 9.2**	**49.8 ± 10.3**	**55.6 ± 8.9**	**56.7 ± 5.6**	**49.8 ± 10.0**	**52.6 ± 9.2**
Baseline MELD, Mean ± SD	**28.4 ± 5.4**	**29.3 ± 5.0**	**27.1 ± 5.8**	**27.5 ± 4.8)**	**27.9 ± 5.5**	**28.5 ± 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

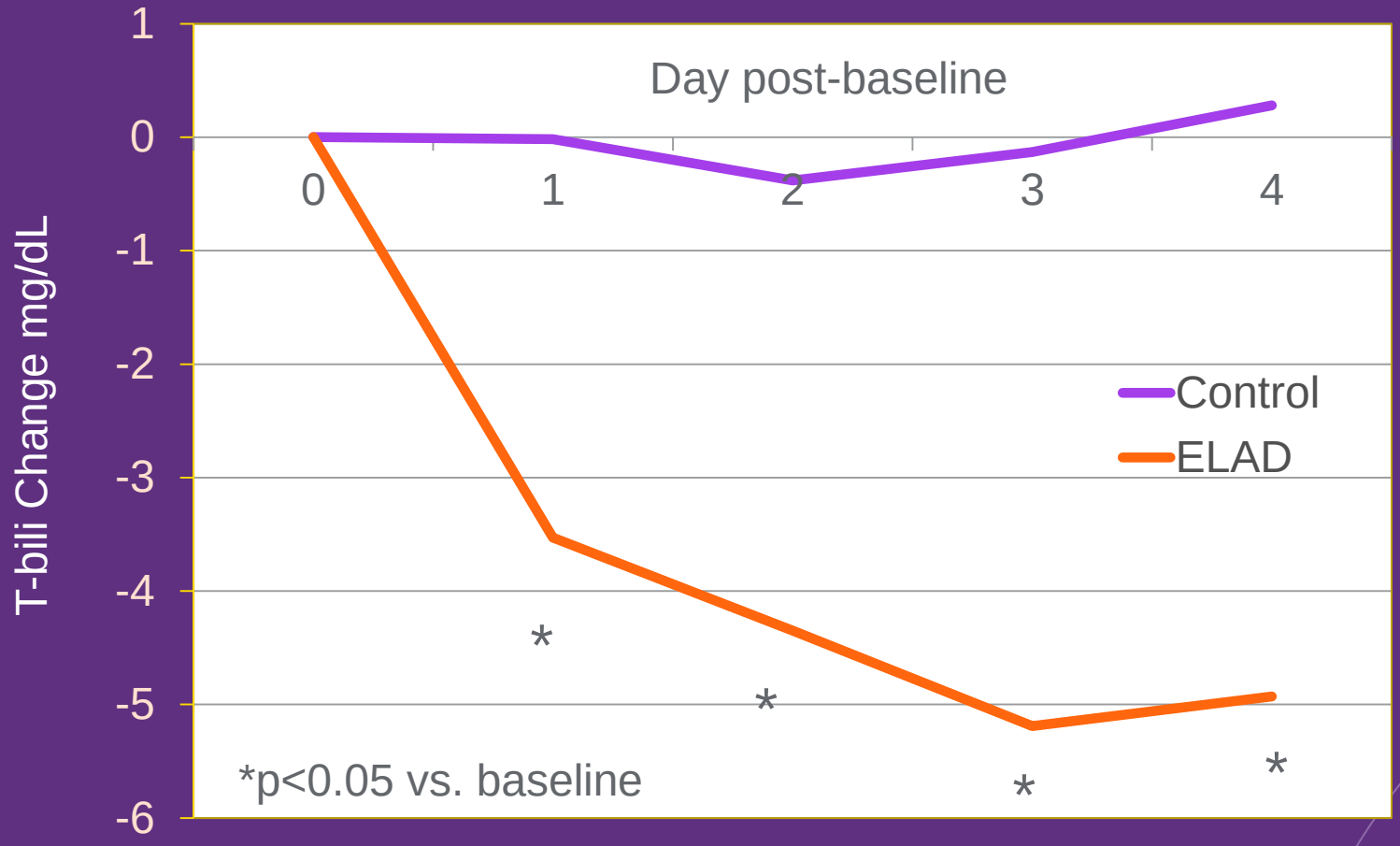
	MITT		PP	
	ELAD n = 9	Control n = 11	ELAD n = 6	Control n = 10
OS through Day 90	2 (22.2%)	6 (54.5%)	**1 (17%)**	**6 (60%)**

- **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)



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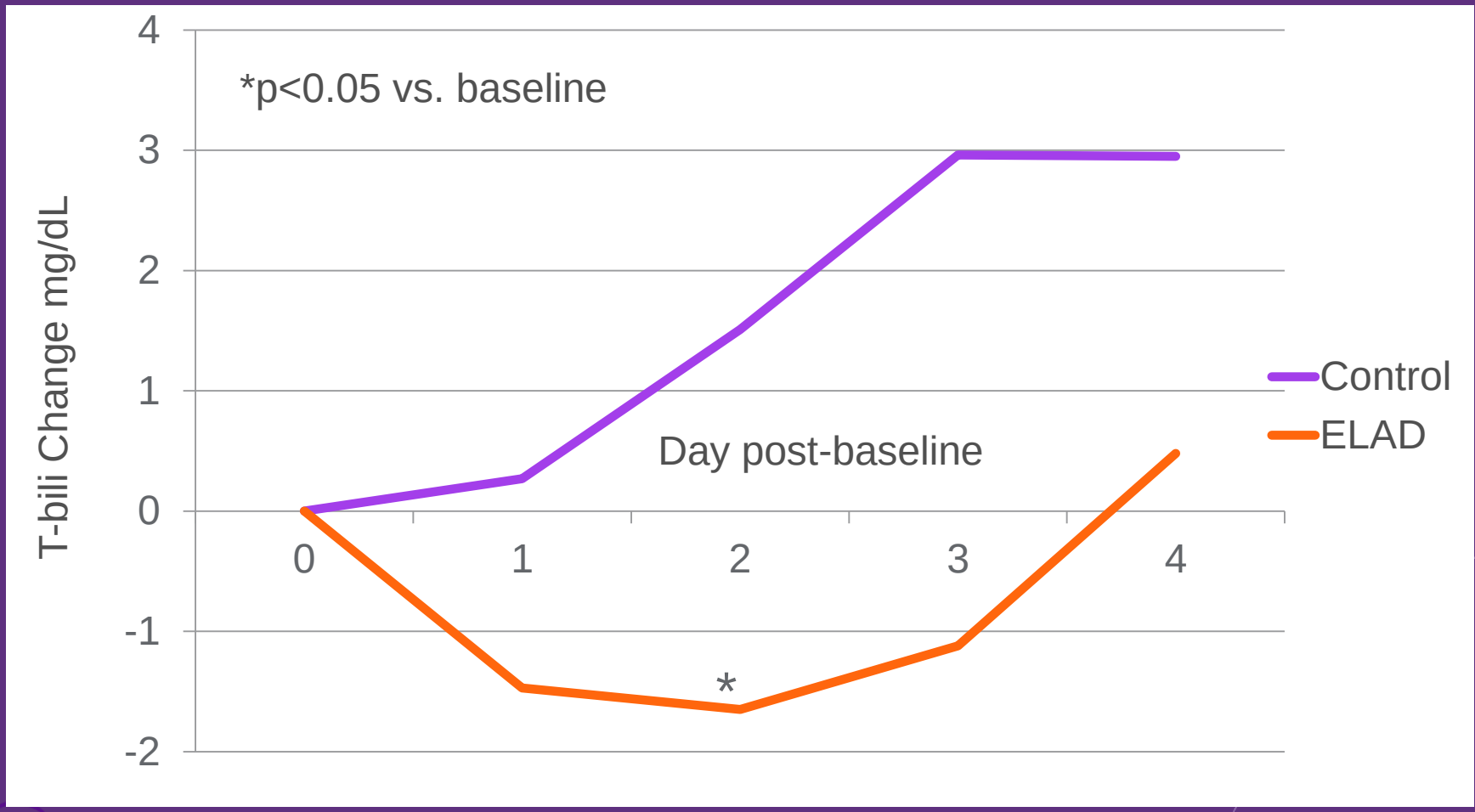
Change in serum t-bilirubin (mg/dL) during treatment Non-AAH Cohort, per-protocol (n=16)



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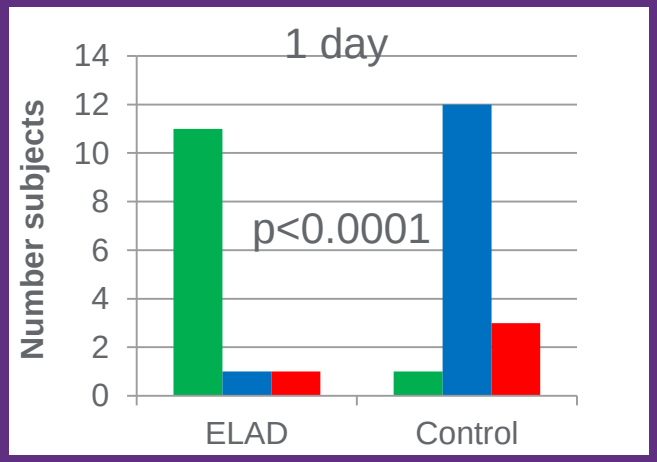
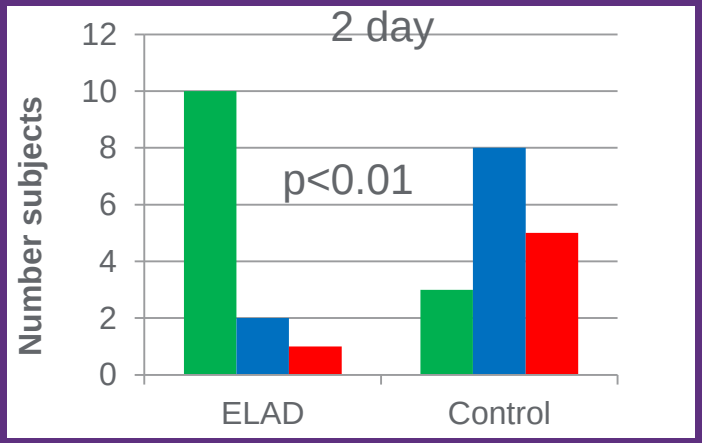
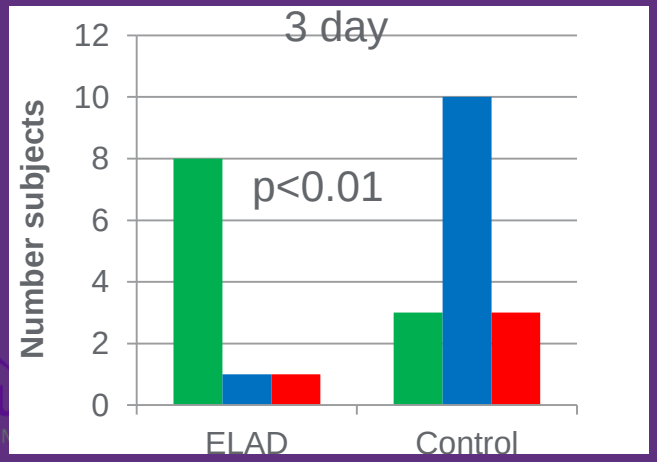
Subject changes vs baseline in serum bilirubin during ELAD therapy: AAH Cohort, per-protocol (n=29)

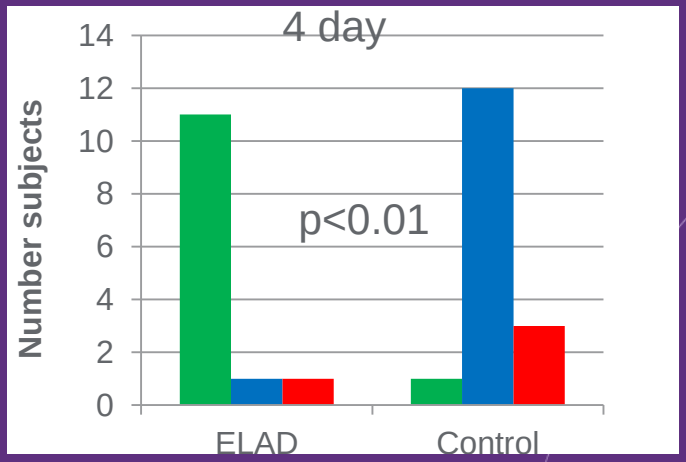
- # subjects with > 10% improvement
- # subjects with < 10% change in either direction
- # subjects with > 10% worsening

p-values are chi-square vs control





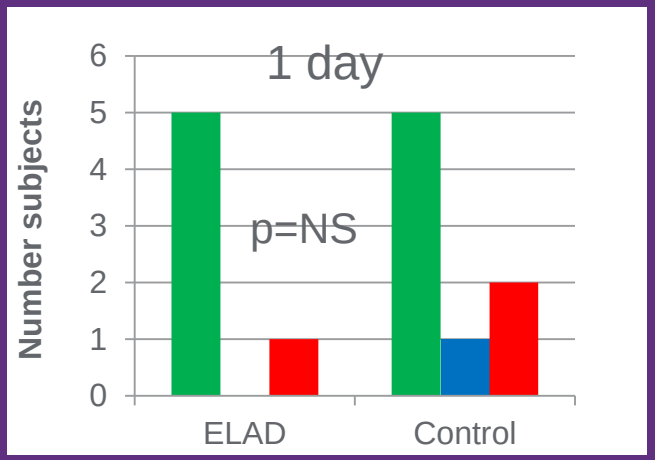


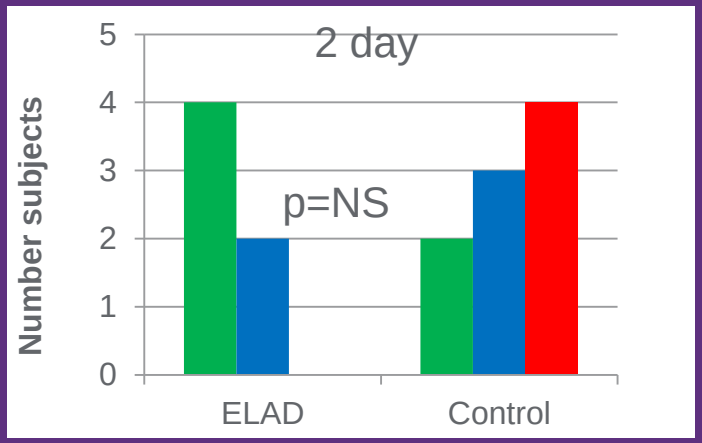


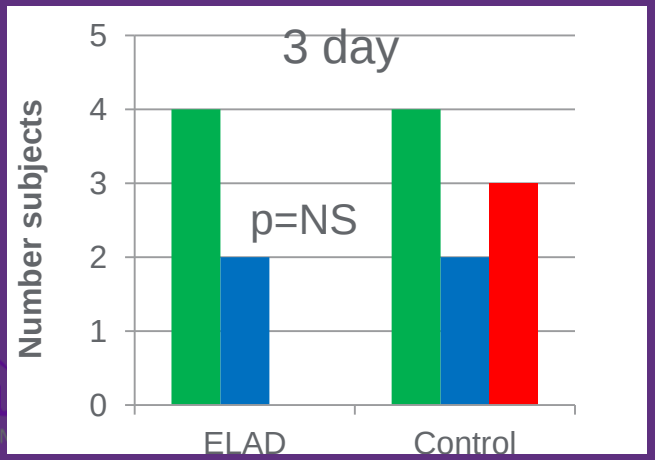
Subject changes vs baseline in serum bilirubin during ELAD therapy: Non-AAH Cohort, per-protocol (n=15)

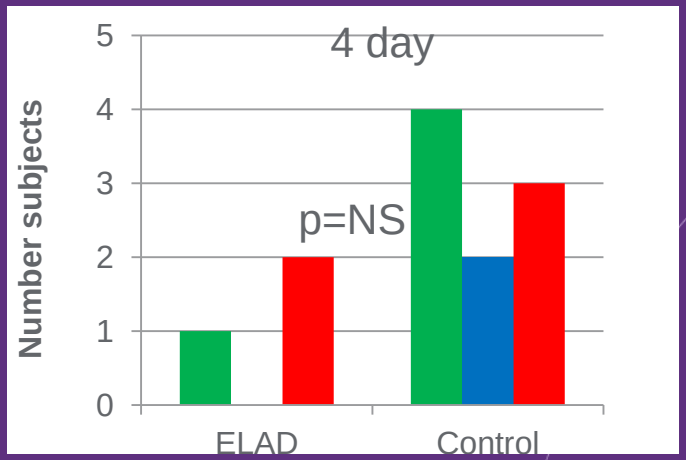
- # subjects with > 10% improvement
- # subjects with < 10% change in either direction
- # subjects with > 10% worsening

p-values are chi-square vs control

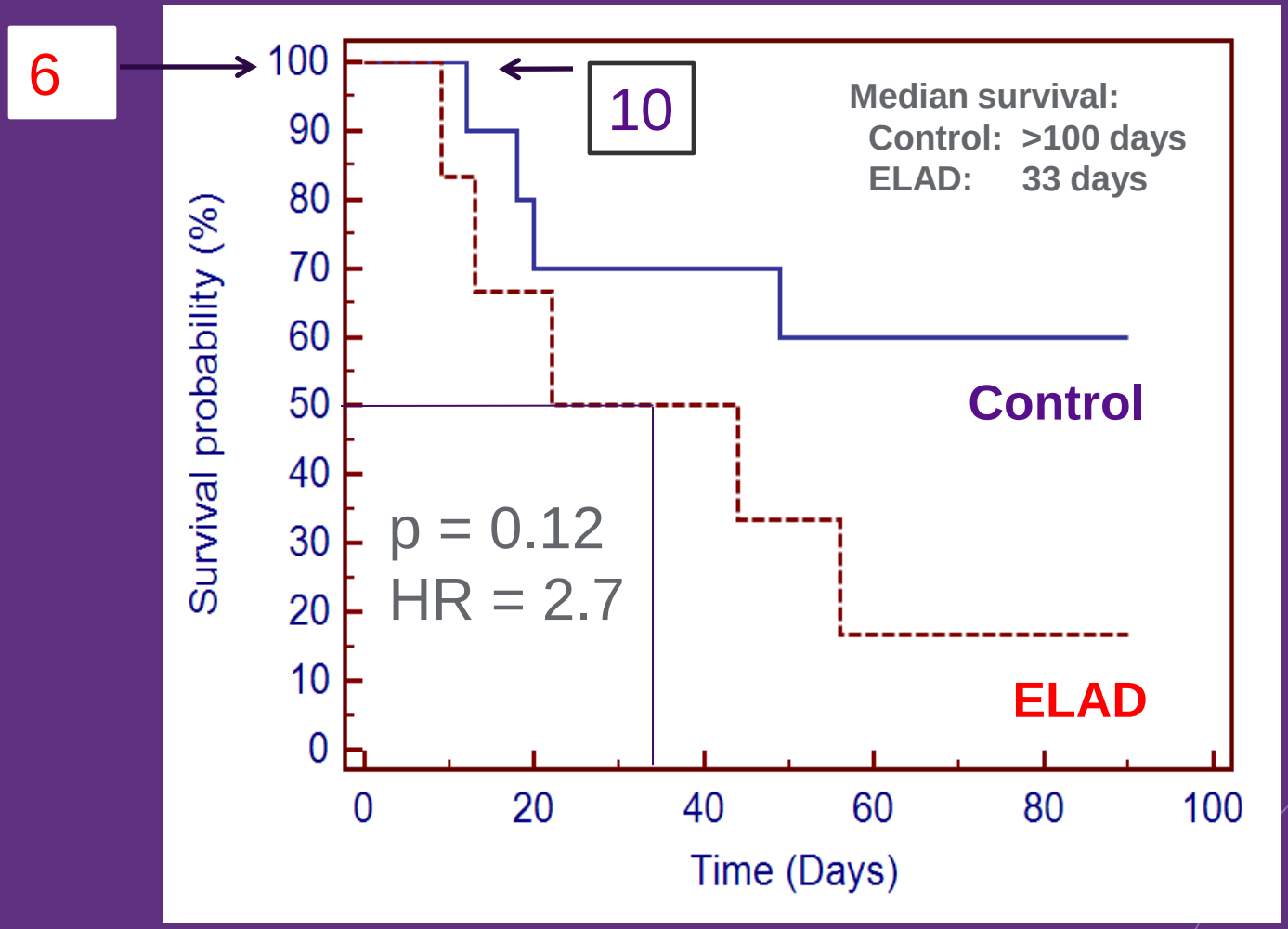




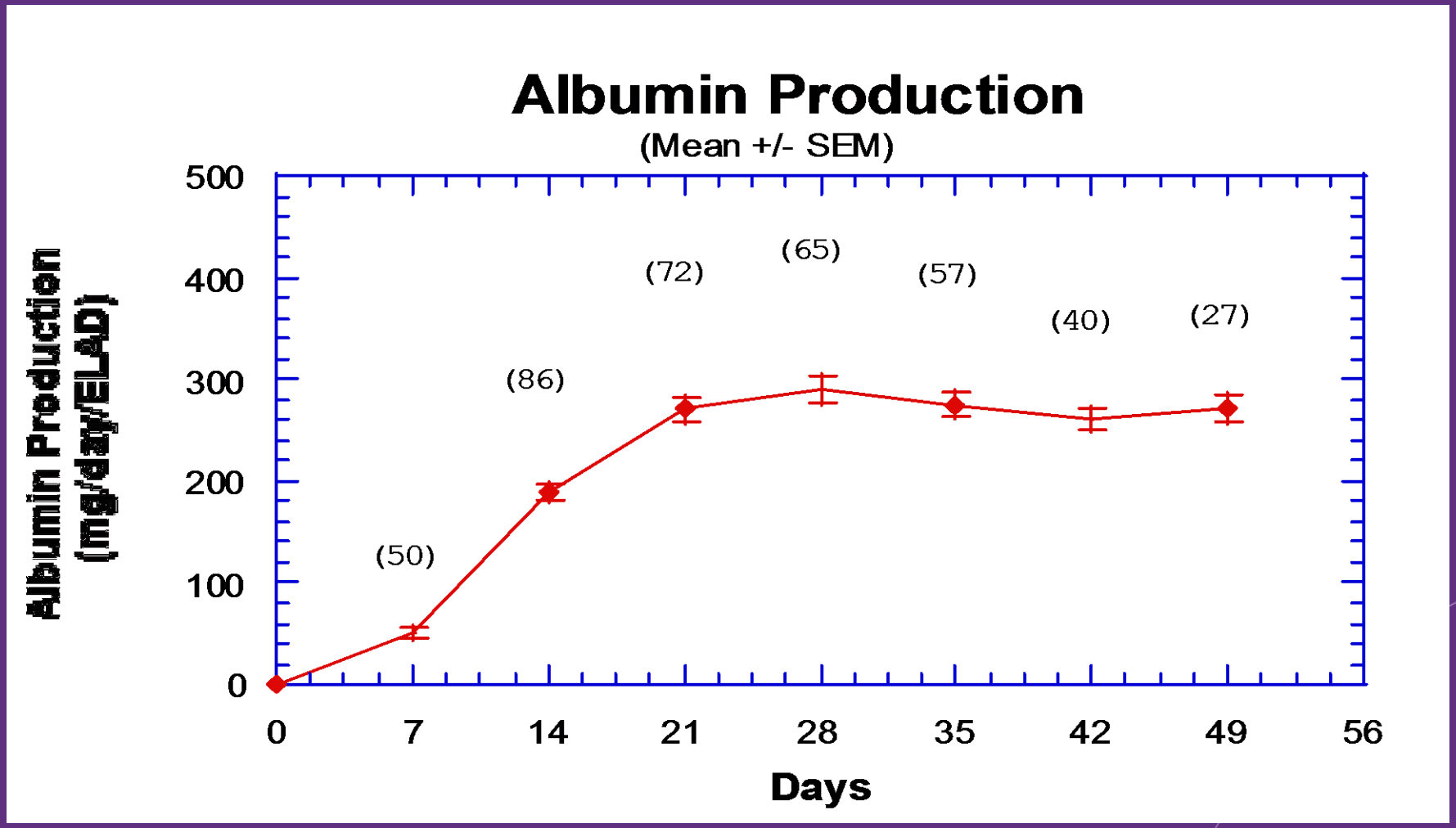




Efficacy: Non-AAH Cohort, per-protocol (n=16)



Albumin Production by Single ELAD® Cartridge In-Process Manufacture



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