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64th Annual Scientific Session & Expo

A Prospective Comparison of Algisyl-LVR with Standard Medical Therapy to Determine Impact on Functional Capacity and Clinical Outcomes in Patients with Advanced Heart Failure (AUGMENT-HF Trial)

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On behalf of the AUGMENT-HF Trial Investigators

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SAN DIEGO
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Disclosures

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Stefan D Anker

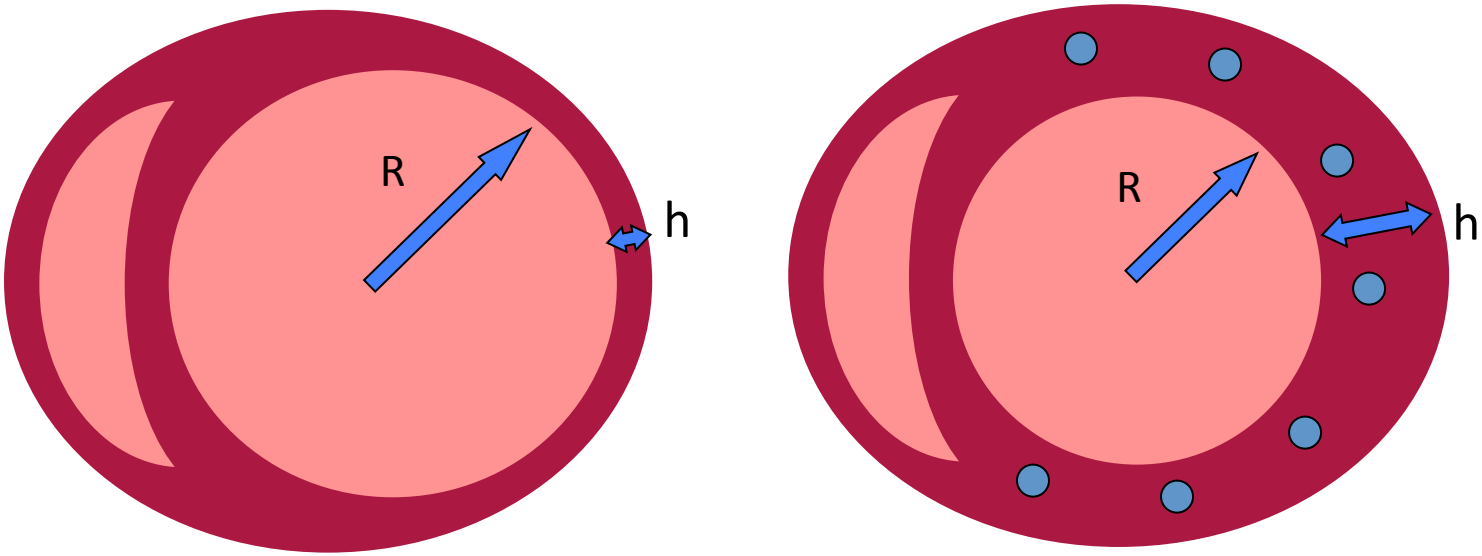
- Scientific Advisory Board – Lone Star Heart, Impulse Dynamics, Respicardia,
- Consultant – Lone Star Heart, Bioventrix, Cardioxyl, Impulse Dynamics, Respicardia, Vifor International
- Grant Support – Abbott Vascular, Vifor International

Background

- Therapeutic options are limited for patients with advanced heart failure who become refractory to conventional pharmacological therapies
- The injection of biomaterials into diseased myocardium has been shown to reduce myofiber stress, LV wall stress, restore LV geometry and improve LV function (animals)
- Algisyl (Algisyl-LVR™) is a medical device that consists of an alginate hydrogel that is injected into the midwall of the LV, where it remains as a permanent implant that is intended to reduce LV wall stress and prevent or reverse the progression of HF
- In a prior phase I pilot study of Algisyl in patients with symptomatic heart failure undergoing CABG, there were significant improvements in cardiac function and reverse LV remodeling observed within 3 months

LV Restoration & Laplace's Law

The mechanism of the Algisyl®



Dilated

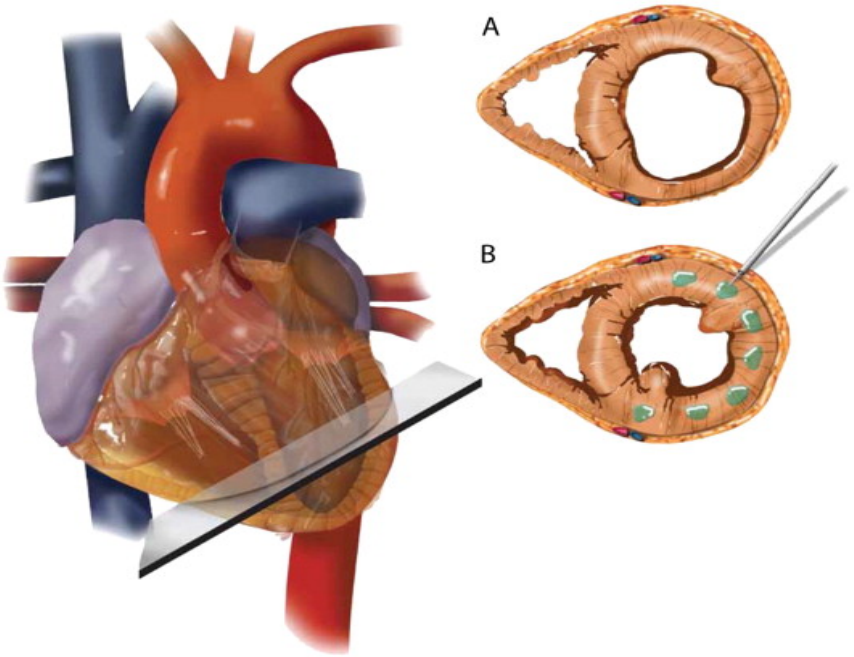
$$\sigma = \frac{P \times R}{2h}$$

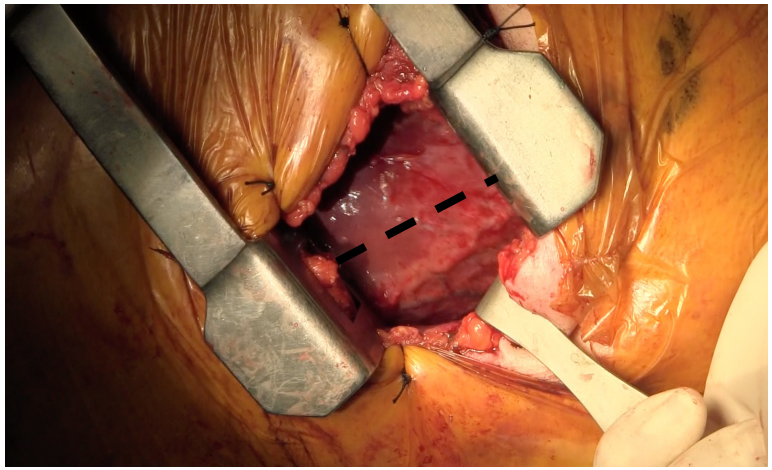
Modified (LVR)

$$\sigma = \frac{P \times R}{2h}$$

LV Restoration with Algisyl

Placement of Alginate Hydrogel via a Limited Thoracotomy





AUGMENT-HF Study Design & Objectives

- Multicenter prospective randomized clinical trial
- 78 Patients with moderate to severe HF (highly symptomatic) that had been treated with optimal medical and/or device therapy, randomized 1:1
  - 40 patients randomized to Algisyl implant procedure + optimal medical therapy
  - 38 patients randomized to optimal medical therapy alone
- 15 centers in Australia, Italy, Romania, Netherlands & Germany
- Primary Efficacy Endpoint: peak VO_2 at 6 months assessed by blinded core lab
- Safety Assessments: clinical outcomes over 30 days, 6, 12 and 24 months
- Secondary Endpoints: symptoms, 6min-WT & cardiac function during follow-up

AUGMENT-HF Key Inclusion & Exclusion Criteria

- Inclusion criteria
  - ischemic or non-ischemic HF patients who remain symptomatic despite optimal evidence-based therapies for HF
  - LVEF ≤ 35%
  - Peak VO_2 of 9.0 - 14.5 mL/min/kg
  - LVEDDi 30 to 40mm/m^2 (LVEDD/BSA)
  - Stable, evidence-based therapy for heart failure
  - Written informed consent
- Exclusion criteria were typical for patients with advanced heart failure
  - Acceptable renal, hepatic, stroke and MI status
  - LV wall thickness of at least 8 mm required for implant

AUGMENT-HF Committees and Core Labs

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Cardiopulmonary Exercise Testing - Henry Ford Hospital (Detroit)
Holter - BioClinica, Inc. Cardiovascular Services (Princeton)
Blood & Biomarkers – ICON Laboratory Services (Dublin, IE)

AUGMENT-HF Baseline Demographics

	All (N=78)	*Algisyl-LVR (N=40)*	*Usual Care (N=38)*
Age (Years)	**62.3 ± 9.6**	*62.6 ± 10.0*	*62.1 ± 9.2*
Gender (Male)	**66 (85%)**	*32 (80%)*	*34 (90%)*
Ischemic HF	**45 (58%)**	*23 (58%)*	*22 (58%)*
Non-ischemic HF	**33 (42%)**	*17 (43%)*	*16 (42%)*
NYHA class - mean	**2.9 ± 0.5**	*2.9 ± 0.4*	*2.8 ± 0.5*
Class II/III/IV	14 / 58 / 5*	*5 / 32 / 2**	*9 / 26 / 3*
LVEF (%)	**25.8 ± 5.5**	*25.6 ± 5.6*	*26.0 ± 5.3*
Peak VO_2 (mL/min/kg)	**12.2 ± 1.8**	*12.2 ± 1.9*	*12.2 ± 1.8*
6 MWT (m)	**295 ± 83**	*280 ± 84*	*310 ± 80*
Atrial fibrillation/flutter	**33 (42%)**	*14 (35%)*	*19 (50%)*
Mitral regurgitation ≥ 3+	**38 (52%)**	*16 (43%)*	*22 (61%)*
Hypertension	**44 (56%)**	*23 (58%)*	*21 (55%)*
Diabetes	**30 (39%)**	*13 (33%)*	*17 (45%)*
Stroke (CVA)	**9 (12%)**	*4 (10%)*	*5 (13%)*
Previous PCI or CABG	**25 (32%)**	*13 (33%)*	*12 (32%)*

* One observation not reported

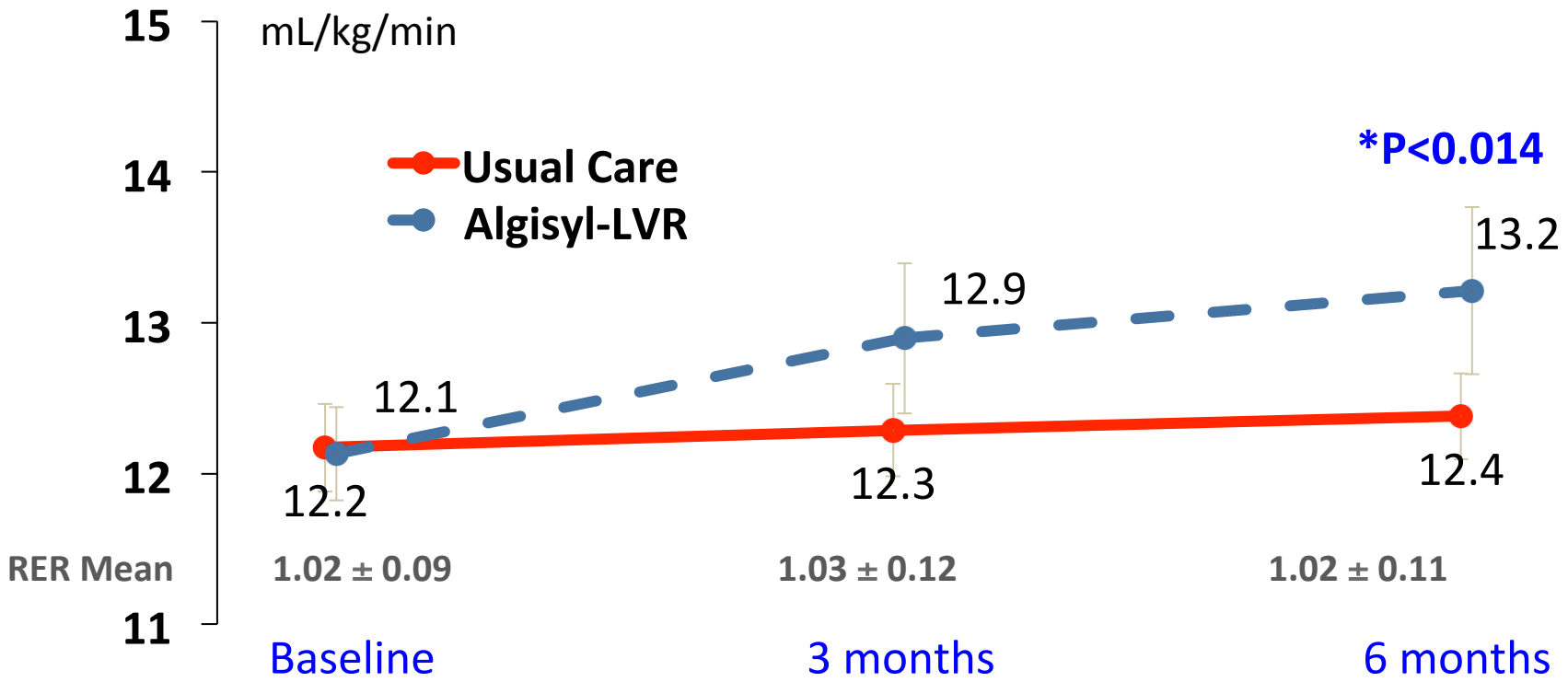
Baseline HF Medications

Medication Class	All (N=78)	*Algisyl-LVR (N=40)*	*Usual Care (N=38)*
Diuretics	**77 (99%)**	*39 (98%)*	*38 (100%)*
Beta-blockers	**74 (95%)**	*37 (93%)*	*37 (97%)*
ARB/ ACE	**69 (89%)**	*34 (85%)*	*35 (92%)*
Aldosterone antagonists	**54 (69%)**	*29 (73%)*	*25 (66%)*
Lipid-lowering	**56 (72%)**	*29 (73%)*	*27 (71%)*
Anti-thrombotics or Anti-platelet agents	**77 (99%)**	*39 (98%)*	*38 (100%)*
Anti-platelet aggregation agents	**52 (68%)**	*31 (80%)*	*21 (55%)*

Operative Procedure Metrics for Algisyl-LVR Implant

	Algisyl-LVR (N=35)
Mean Anesthesia duration (min)	190 ± 29
Mean Procedure duration (min)	80.5 ± 24.9
Mean Total number of Algisyl-LVR implants (injections)	15.5 ± 2.0
Mean Total volume of polymer administered (mL)	4.6 ± 0.6
Mean ICU Length of Stay (days)	4.3 ± 7.3
Median ICU Length of Stay (days)	*2.0 (1.0 – 43.0)*

AUGMENT-HF – Change in Mean Peak VO_2



AUGMENT-HF Primary Endpoint

Change in Peak VO_2 at 6 months

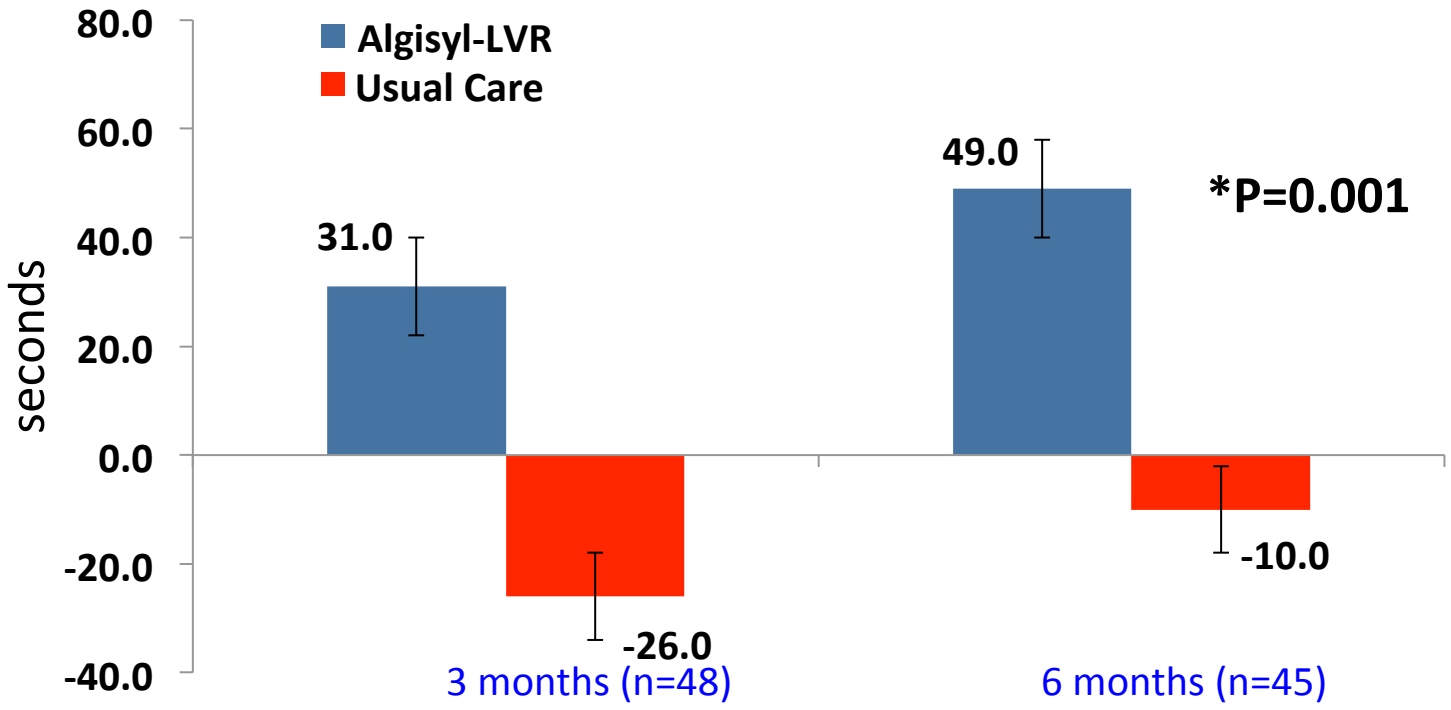
Repeated measures mixed model with dependent variable as Peak VO_2 and independent variables as baseline Peak VO_2 value, study group (Algisyl-LVR, Usual care), follow-up time 3 & 6 months and treatment-by-time with an unstructured covariance matrix to model the within-patient variability.

Peak VO_2 (mL/min/kg)			
Adjusted mean [95%CI]			
Usual Care (N=38)	Algisyl-LVR (N=40)	Mean product effect [95%CI]	P
12.2 [11.6 ; 12.9]	13.5 [12.8 ; 14.2]	1.24 [0.26 ; 2.23]	0.014

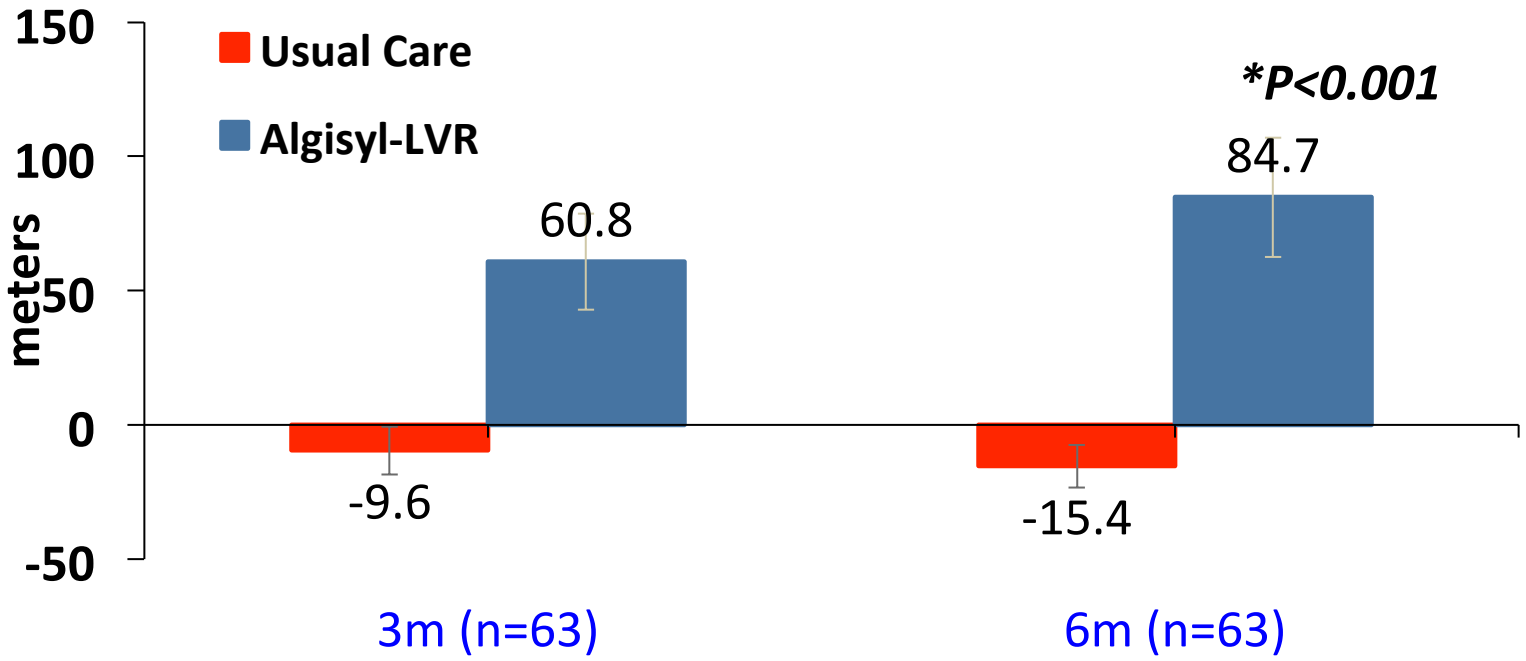
AUGMENT-HF – Subgroup analyses for primary endpoint

	Usual Care	Algisyl	Mean Treatment effect on Peak VO2 [ml/min/kg]	P-value	Interaction P-value
Overall	*38*	*35*	*1.24 [0.26 ; 2.23]*	*0.014*	
Baseline Median peak VO2					
< 12.5 mL/min/kg	19	18	1.19 [0.15 ; 2.24]	0.027	0.231
≥ 12.5 mL/min/kg	18	16	1.23 [-0.37 ; 2.83]	0.127	
Baseline Median 6MWT					
< 287m	20	15	2.42 [0.77 ; 4.07]	0.006	0.014
≥ 287m	18	20	0.42 [-0.90 ; 1.73]	0.520	

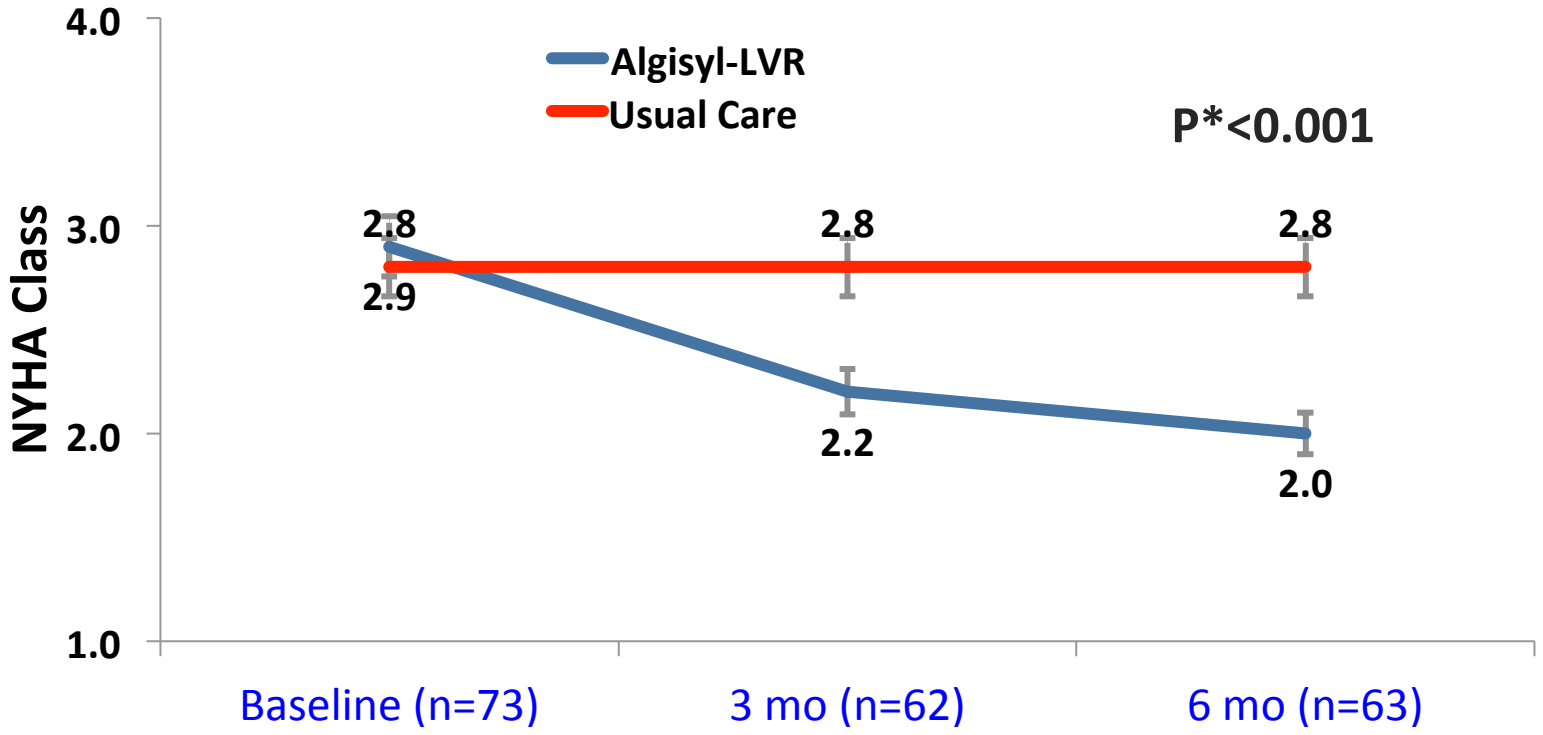
AUGMENT-HF – Exercise Time (CPX), change from baseline



AUGMENT-HF 6min-WT - change from baseline



NYHA Functional Class – continuous representation



AUGMENT-HF - Summary of Clinical Outcomes

Outcomes	Mean Difference Algisyl-LVR vs. Standard Medical Therapy	P Value Algisyl-LVR vs. Standard Medical Therapy
Peak VO_2 (mL/kg/min)	1.24	0.014
Peak Watts	10.2	0.001
Total Exercise Time (min)	0.97	0.001
6-min walk test distance (m)	141[a]	< 0.001
NYHA class	- 0.9	< 0.0001

[a] *non-parametric test*

AUGMENT-HF Safety End Points

Effect of Algisyl-LVR on 30 day mortality

- The pre-specified estimate of death within 30 days was 5%, based upon literature of similar surgical device trials.
- The 95% CI (binomial distribution) for this estimate was 1.80% - 23.06%, provided that < 4 deaths were observed in the study during 30 days

- The actual number of deaths observed in 30 days was 3 (8.57%)
- Based upon the pre-specified data analysis plan the primary safety endpoint of AUGMENT-HF was met.

All Adverse Events – up to 6 months post-randomization

Safety population	Usual Care (N=38)		Algisyl-LVR (N=40)			
	Total # of events	# of patients with events (%)	Total # of events	# of patients with events (%)	HR (95% CI)	P
All adverse events	63	17 (44.7)	115	31 (77.5)	3.41 (1.87 - 6.22)	<0.001
Serious adverse events	26	10 (26.3)	33	16 (40.0)	2.08 (0.94 - 4.60)	0.063

Adverse Events, MACE & Death – CEC Adjudicated

Safety population	Usual Care (N=38)		Algisyl-LVR (N=40)	
Event	Total # of events	# of patients (%)	Total # of events	# of patients (%)
Death	3	3 (7.9%)	6	6 (15.0%)
Cardiovascular death	3	3 (7.9%)	5 *	5 (12.5%)
Adverse events within 30 days after surgery	.	NA	68	22 (55.0%)
Minor surgical complication	.	NA	43	18 (45.0%)
Major surgical complication	.	NA	18	10 (25.0%)
MACE events (All MACE events)	22	10 (26.3%)	18	11 (27.5%)
MACE events (excluding index hospitalization)	**22**	**10 (26.3%)**	**9**	**7 (17.5%)**
Cardiovascular death	**3**	**3 (7.9%)**	**3**	**3 (7.5%)**
Cardiac arrest	**1**	**1 (2.6%)**	**1**	**1 (2.5%)**
Worsening heart failure	**14**	**8 (21.1%)**	**5**	**4 (10.0%)**
Sustained ventricular arrhythmias	**4**	**4 (10.5%)**	**1**	**1 (2.5%)**

* Two adjudicated CV deaths after 30 days:
  - One patient death following heart transplant with acute rejection
  - One patient died of Klebsiella pneumonia, polyneuropathy and systemic sepsis

Conclusions

- The results of the AUGMENT-HF trial demonstrate that Algisyl injections can be administered safely in patients with advanced heart failure, with an acceptable 30 day post-operative morbidity & mortality.
- Treatment with Algisyl provided an improvement in functional capacity and heart failure symptoms when compared to patients in the control group.
- The early evaluation of 6-month MACE suggest a potential favorable impact on reduction of HF hospitalization in patients treated with Algisyl.
- This study provides proof-of-concept for LV augmentation with Algisyl as a potential novel new therapy for patients with advanced heart failure.