Alpharetta (ALP-189) for the Treatment of Chronic Hepatitis C Infection

Events are true - Names and Designations Changed

Eric Hughes, MD, PhD
Head of Clinical Development and Analytics, Novartis
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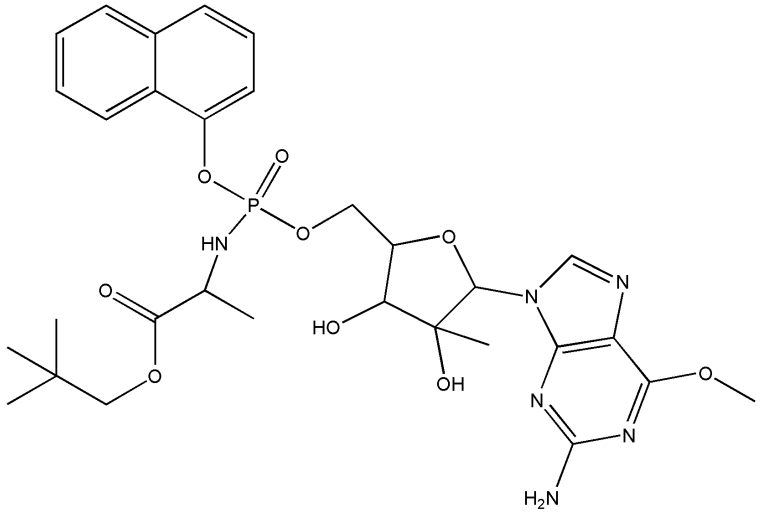
HBV Forum

Alpharetta (ALP-189)

Developed at a small biotech company for anti-HCV therapy

- HCV NS5b nucleoside inhibitor
- Pan-genotypic antiviral activity in vitro
- High genetic barrier to resistance (S282T)

HCV genotype	EC50 (μM)
1 b	0.035
1b	0.010
1a	0.012
2a	0.001
2b	0.001
3a	0.005
4a	0.002



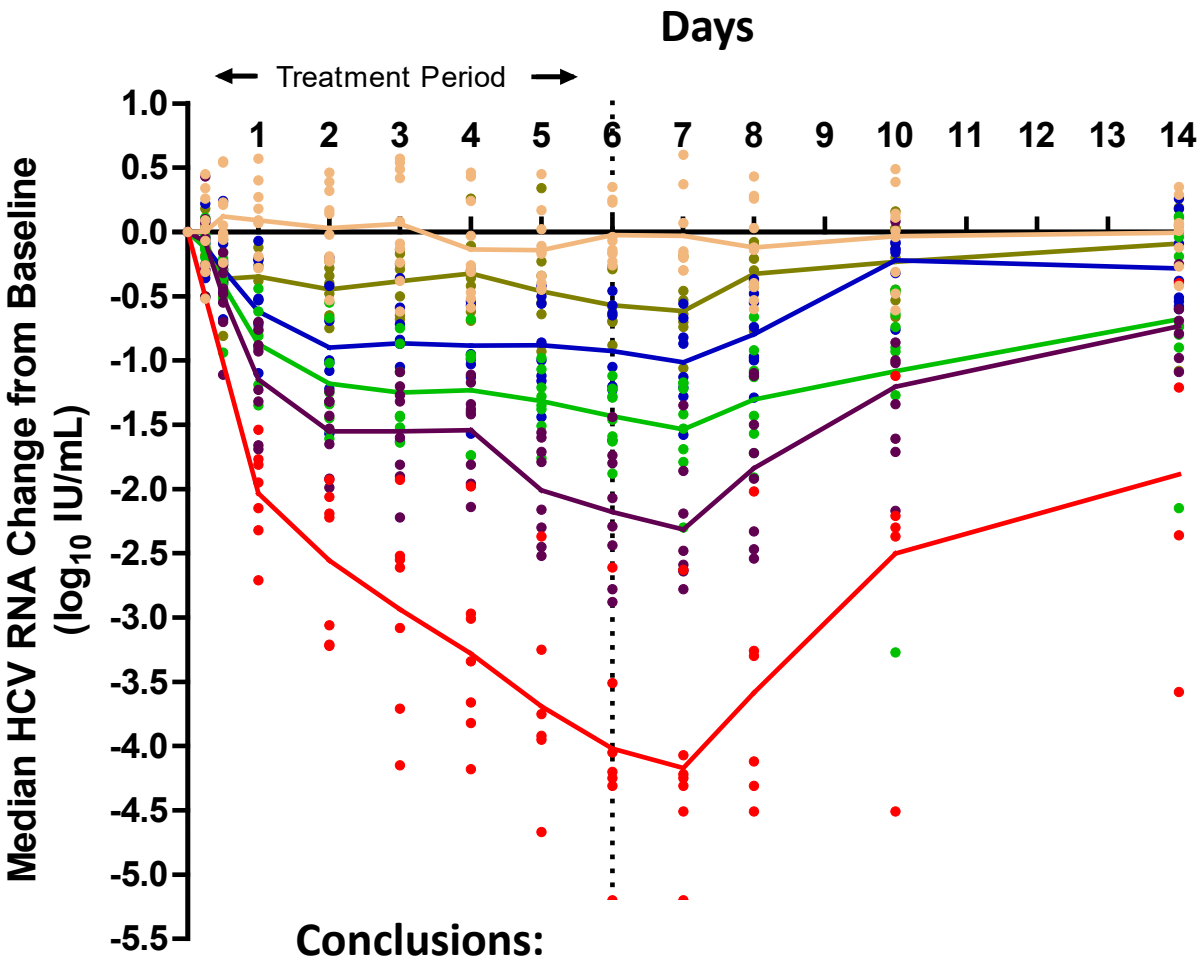
ALP-189 Preclinical Studies

- No effect on hERG currents for ALP-189 or its metabolites in standard preparations of HEK-293 cells
- Effects of high exposures for a 6 month duration at *non-tolerated* doses [150 mg/kg/d in mice/rat] observed multiple target-organ toxicities (skeletal muscle, heart, kidney, GI tract, lymph nodes, and bone marrow)
- Effects at *tolerated* doses [≤25 mg/kg/d in mice/rat (NOAEL); ≤200 mg QD human equivalent dose] were largely limited to minimal skeletal muscle degeneration at low multiples of the projected clinical exposure
- Since skeletal muscle degeneration correlated with increases in standard serum chemistry analytes (eg, transaminases and creatine kinase [CK]), clinical dosing was deemed safe with appropriate monitoring (up to 200 mg QD)
- Troponin monitoring is added for an additional measure of cardiac muscle injury

Alpharetta (ALP-189) Phase 1 Trials

Study number/ Description	Duration (days)	Doses of ALP-189 (mg)	Number of Patients	Patient Characteristics
ALP-189-001/ SAD	1	3, 9, 25, 50, 100	36	Healthy volunteers
ALP-189-002/ MAD	7	9, 25, 50, 100, 200		HCV GT1-infected
ALP-189-004/ DDI (midazolam) No interaction Observed	5-8	50	28	Healthy volunteers
ALP-189-005/ DDI (verapamil) No interaction Observed	12	50	24	Healthy volunteers

Alpharetta (ALP-189) : Multiple-Dose Monotherapy



Median Viral Load Declines after 7 doses

-0.62 log_{10} IU/mL = 9 mg

-1.02 log_{10} IU/mL = 25 mg

-1.53 log_{10} IU/mL = 50 mg

-2.54 log_{10} IU/mL = 100 mg

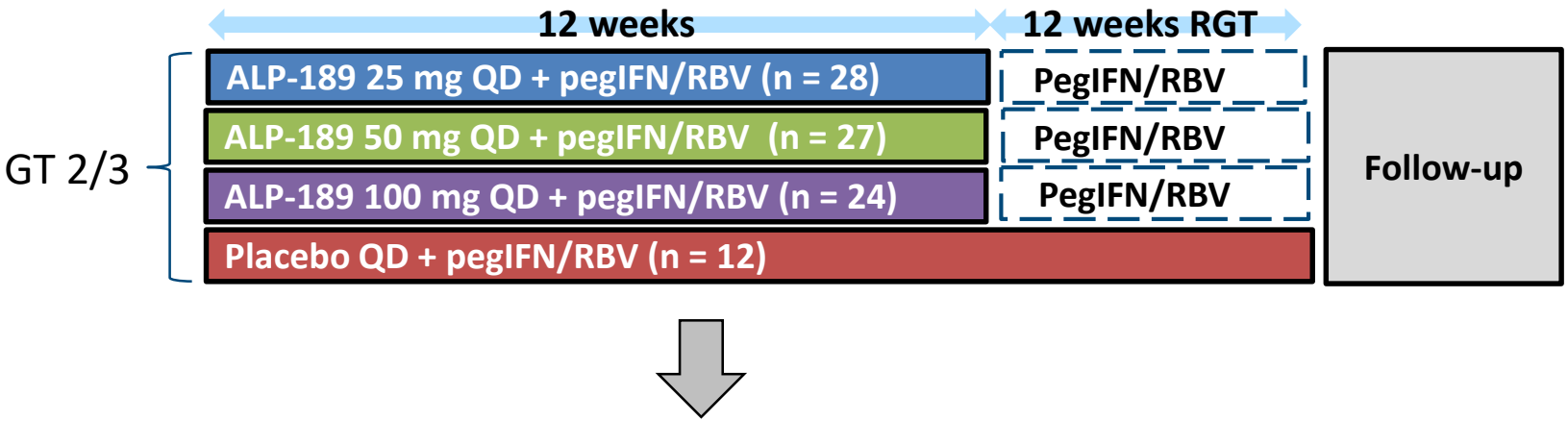
-4.25 log_{10} IU/mL = 200 mg

- Placebo
- 9 mg ALP-189 QD X 7
- 25 mg ALP-189 QD X 7
- 50 mg ALP-189 QD X 7
- 100 mg ALP-189 QD X 7
- 200 mg ALP-189 QD X 7

Conclusions:

- **Well tolerated, no ALT/AST, ECG, CK or Troponin elevations**
- **Dose-dependent antiviral effect with greatest activity at 200 mg QD**

Phase 2 Study Part A: ALP-189 + pegIFN/RBV (N = 91)



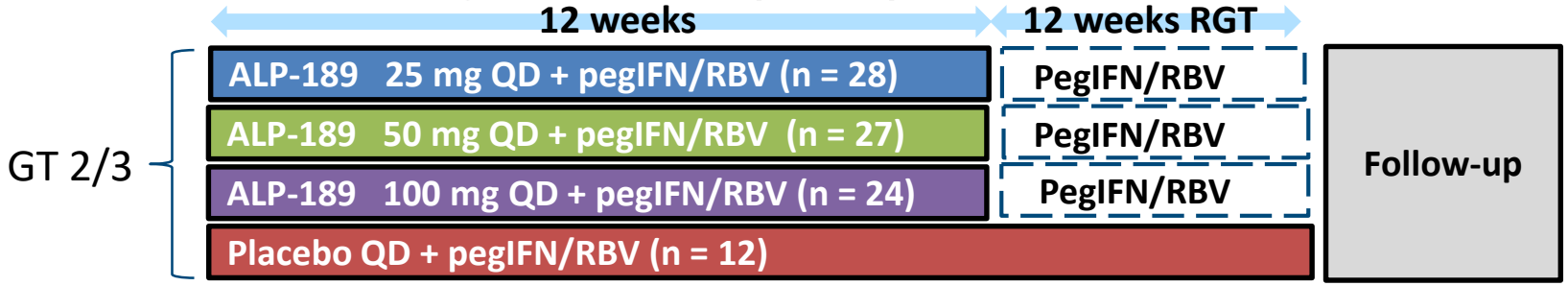
12-Week Interim review by external SRC in June 2012

SUMMARY OF KEY CONCLUSIONS:

- The safety data appeared comparable with pegIFN/RBV
- No treatment emergent ECG readings of safety concern have been noted
- No CK or troponin elevations, no AST/ALT elevations
- **66%** Sustained Viral Response (SVR) achieved with **ALP-189 100 mg QD + pegIFN/RBV** after 12 week triple therapy followed by 12 weeks of PEG/RBV

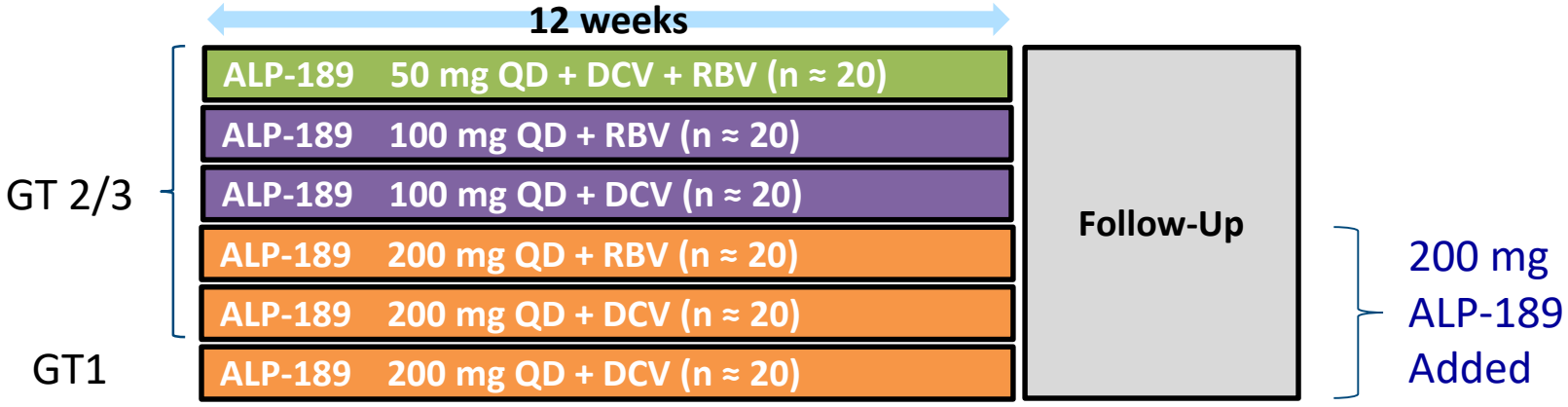
Phase 2 ALP-189-003 Part B: New Study Design to Explore All-Oral Combination Therapy

Part A : ALP-189 + pegIFN + RBV (N=91)



The ongoing study is amended to include Part B

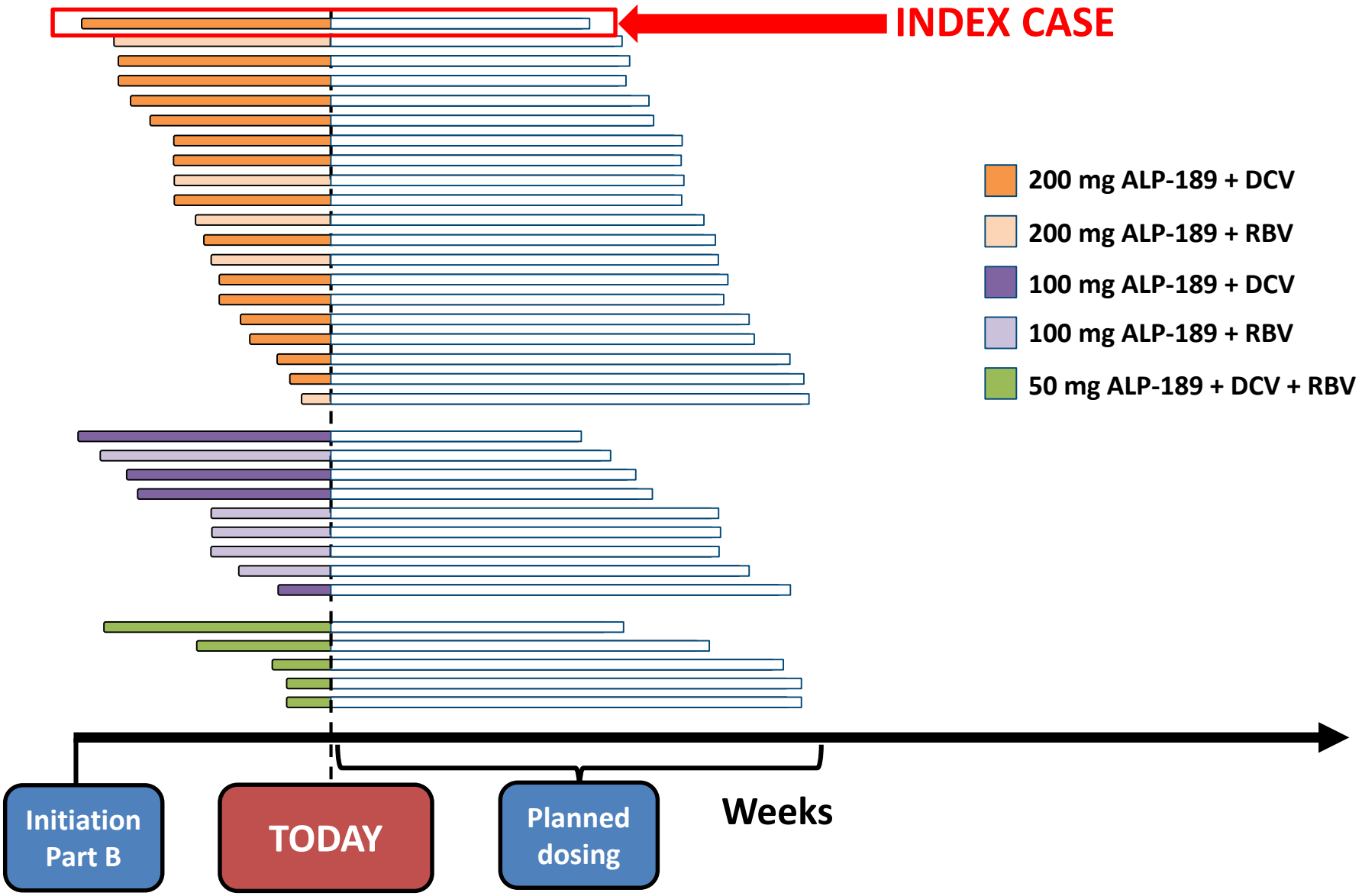
Part B : ALP-189 + daclatasvir (DCV) and/or RBV



Sunday Night (8 PM, July 29th)

- The medical monitor is informed by study site that a 25-year-old white male with a history of chronic HCV infection, opioid dependence, cocaine abuse, and mild depression, who received 200 mg of ALP-189 and DCV for 40 days (~6 weeks) has been admitted to the hospital in cardiogenic shock; no records are immediately available
- No significant clinical events were reported during the initial three on-treatment visits. The Week 2 ECG demonstrated a newly acquired, nonspecific ST abnormality that was considered not clinically significant at the time; creatinine and troponin levels remained within normal limits.
- On Day 39, the patient reported nausea and vomiting and was prescribed prochlorperazine. The following day, he was hospitalized for shortness of breath and was noted to have pulmonary edema, acute renal failure, and shock liver. A TTE demonstrated an LVEF <10%.

Part B: 34 Patients Dosing (Index Case Relative to other Subjects)

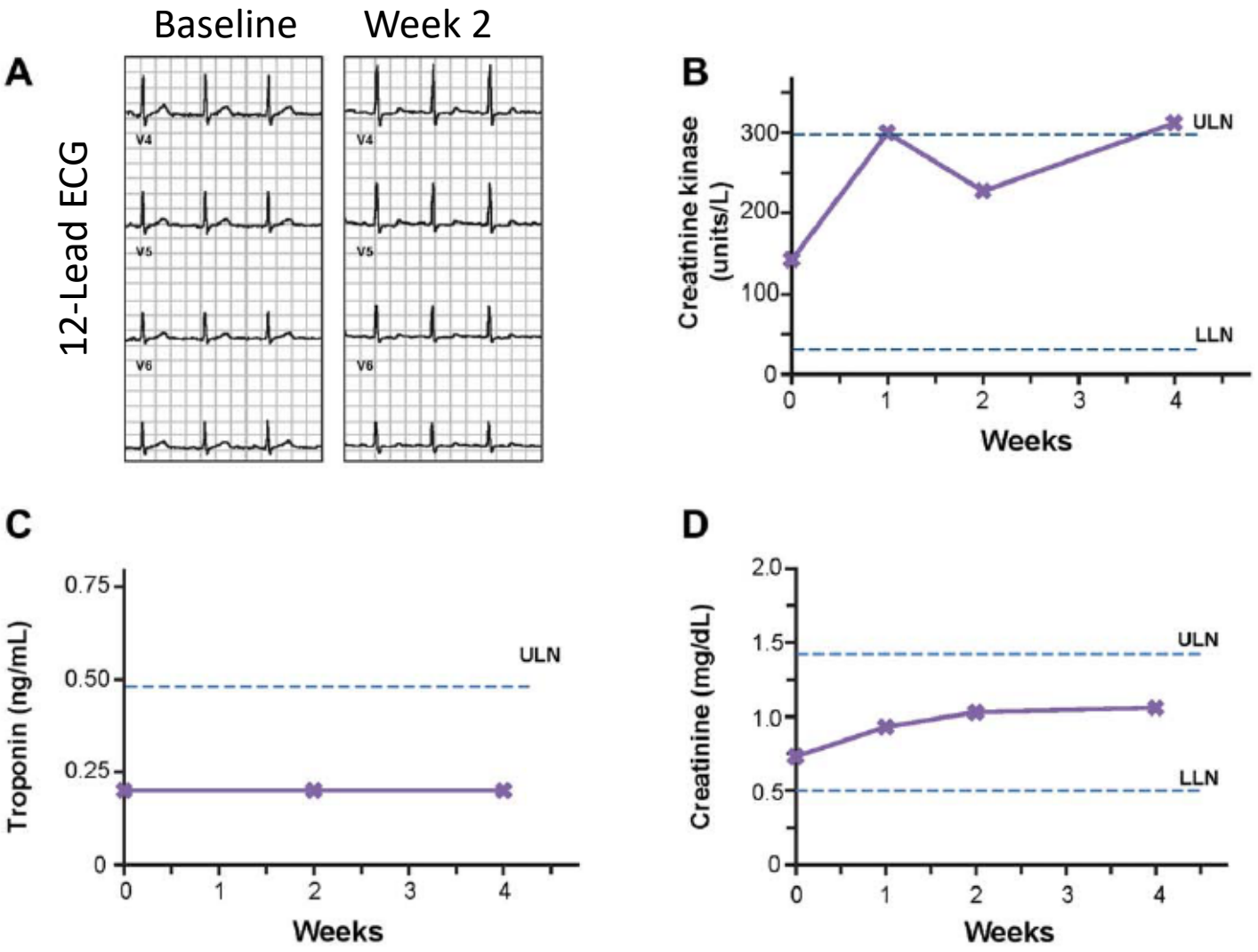


More Information on Index Case (24-36 Hours after First SAE Report)

- Baseline chest X-ray (prior to study) shows mild cardiomegaly.
- Laboratory data on admission to hospital included:
  - Creatine kinase, 397 U/L (normal range: 30-200 U/L);
  - Troponin, 0.02 (normal range: <0.04);
  - Creatinine, 2.3 mg/mL (normal range: 0.7-1.3 mg/dL);
  - ALT, 3,861 IU/L (normal range: 13-69 IU/L);
  - AST, 4,909 IU/L (normal range: 15-46 IU/L).
- Immediate clinical course, escalation in therapy including an intra-aortic balloon pump, extracorporal membrane oxygenation, intravenous, dopamine, and continuous renal replacement therapy.
- Care was withdrawn approximately 2 weeks after initial presentation

Discussion

Index Case Data



Drug Dosing Discontinued Immediately

- July 29 (Sunday evening):
  - The medical monitor informed by study site that index case was hospitalized in ICU for cardiac and multi-organ failure, no records immediately available from hospital
- July 30 (Monday):
  - All available data collected immediately on index case, cardiologists consulted
- July 31 (Tuesday):
  - Reviewed data from study with internal cardiac experts and senior company management
- August 01 (Wednesday)
  - Company decision to suspend study drugs, all investigators immediately informed
  - FDA informed
  - Press release
- August 02 (Thursday)
  - Confirmed all patients off study drugs
- August 03 (Friday)
  - 1st teleconference with FDA, ALP-189 formally placed on clinical hold

Immediate Response and Communication After Termination of Dosing in Part B

- Sites requested to communicate with all patients a minimum of 2x weekly
  - Cardiac ECHO/ECG/labs were requested on a weekly basis
  - ***Multiple cardiac SAEs begin to be reported Monday, August 6th.***
- Company holds teleconferences with each site individually 2x weekly
  - Patient by patient review to discuss monitoring and care
  - Low threshold for immediate referral to a tertiary care center
  - Company obtained permission from patients for direct phone support system
  - Company letter provided to patients information and emergency contact
- FDA
  - weekly teleconferences and face to face meeting
  - monthly reports provided to FDA
- "Data sharing room" established for FDA, medical consultants, and external companies

Collaboration with Duke Clinical Research Institute (DCRI)

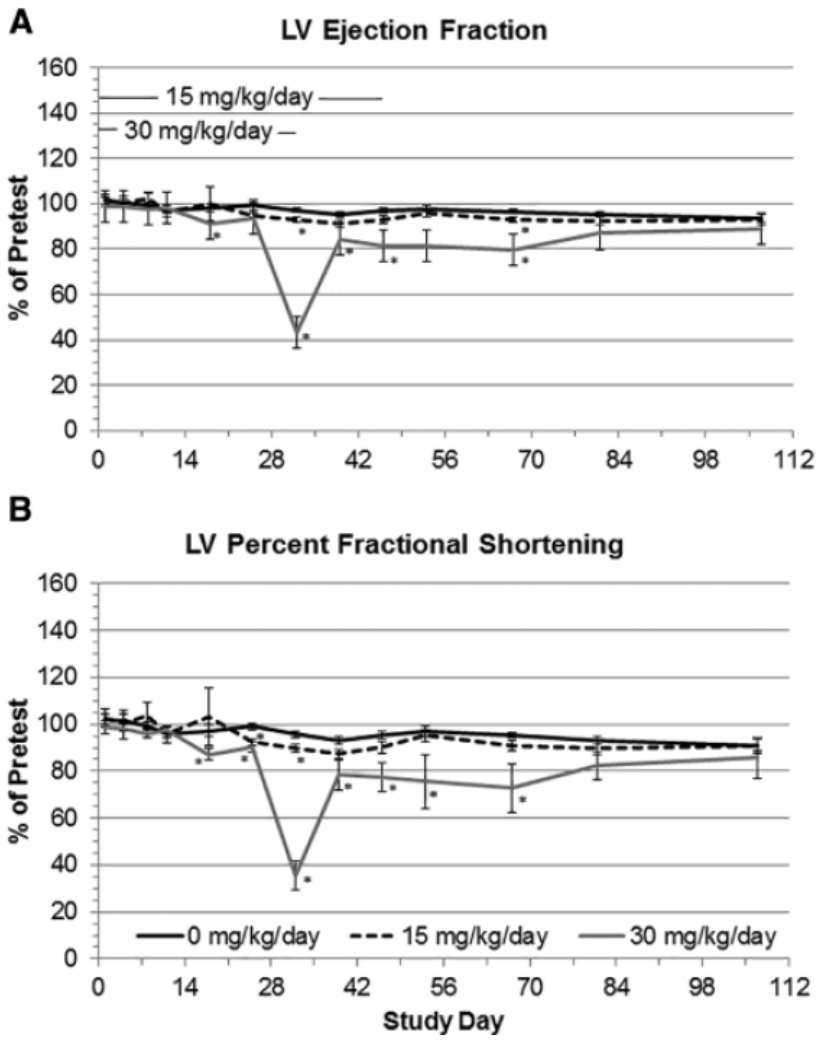
- DCRI collaboration provided external expertise in patient management
- DCRI established CHF Centers of Excellence Referral Network for patients exposed to ALP-189
- Established observational protocol for longitudinal assessment of patients
  - Enrollment offered to patients from all ALP-189 studies
  - 5 year study to monitor the cardiovascular and renal health of APL-189 exposed patients compared to cohort of HCV-infected patients without ALP-189 exposure
  - Ongoing evaluation of ECHO, ECG, biomarkers

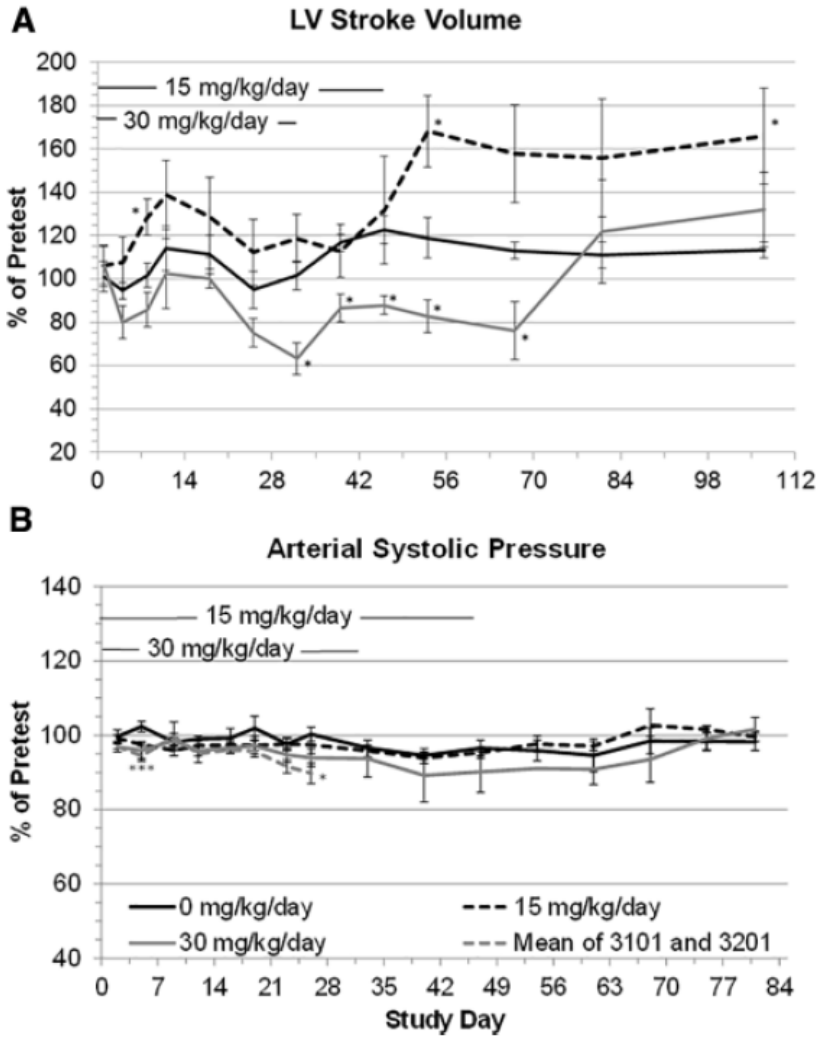
Crisis Management
Lessons Learned

- Preclinical data can be highly exposure & species specific
- Nothing replaces informed and attentive medical monitoring
- Consult specialty medical experts immediately in a crisis
- The well-being of subjects must guide all decisions
- Communication both internally and externally is critical
- Collaboration and sharing of data should become standard

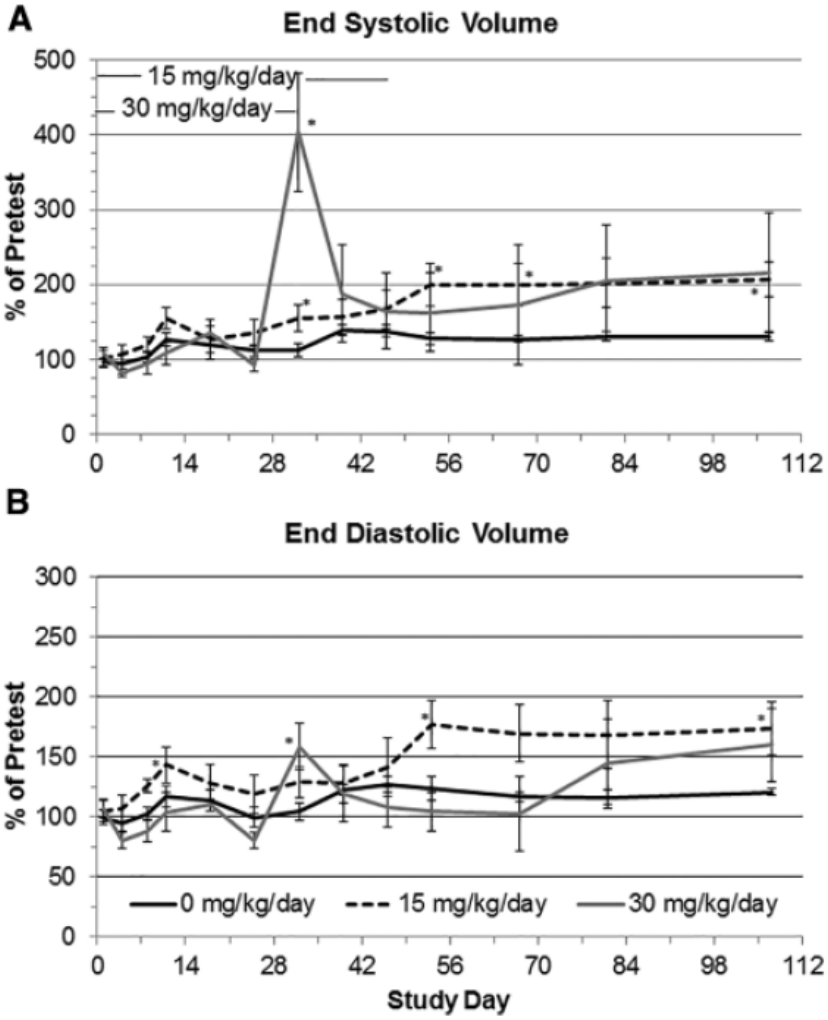
Follow-up Studies

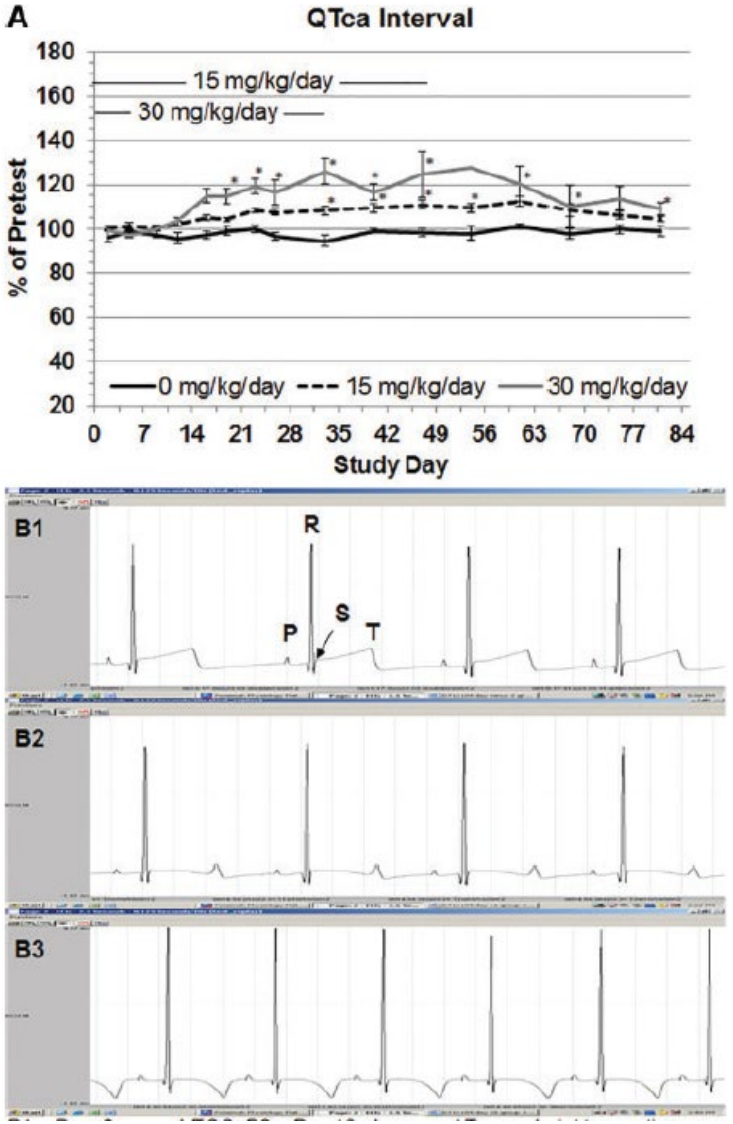
Follow-up Non-Human Primate CV Study





Follow-up Non-Human Primate CV Study

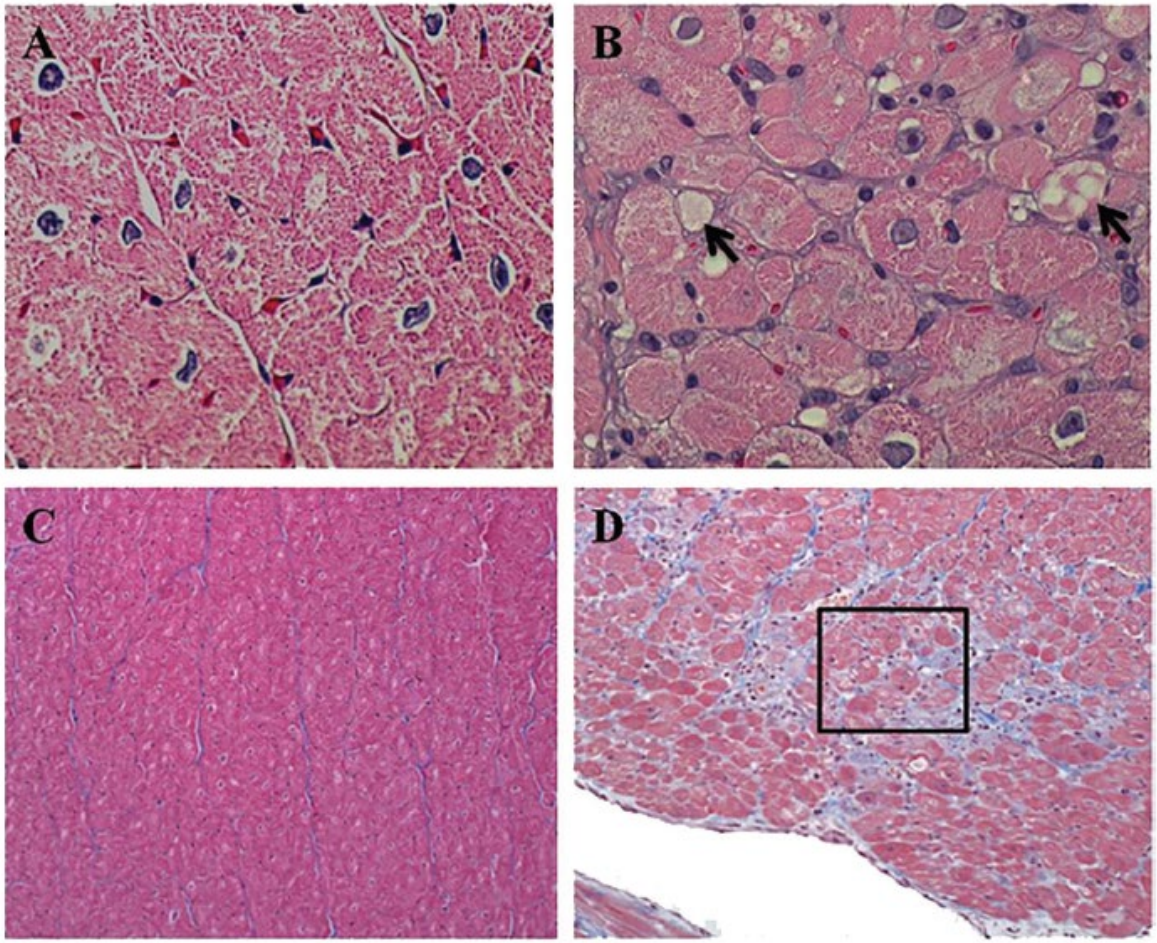




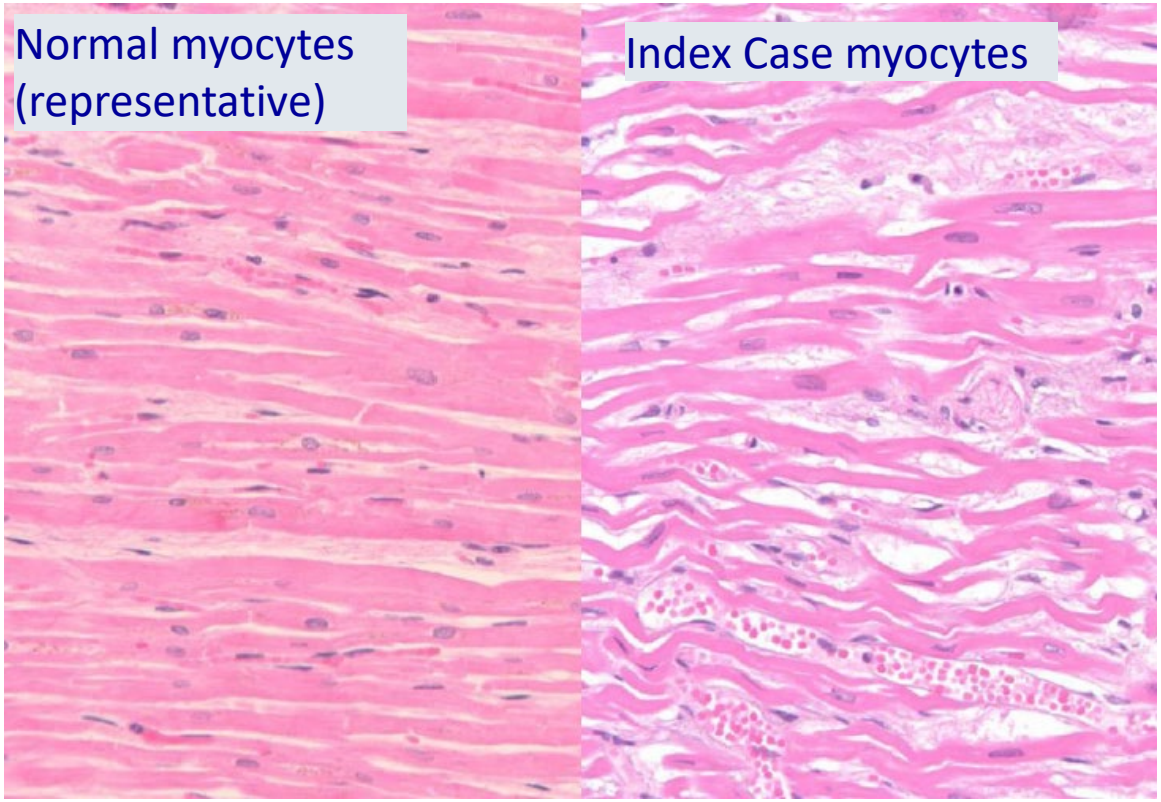
Follow-up Non-Human Primate Cardiac Histopathology

Control Monkey

ALP-189



Index Case Histopathology

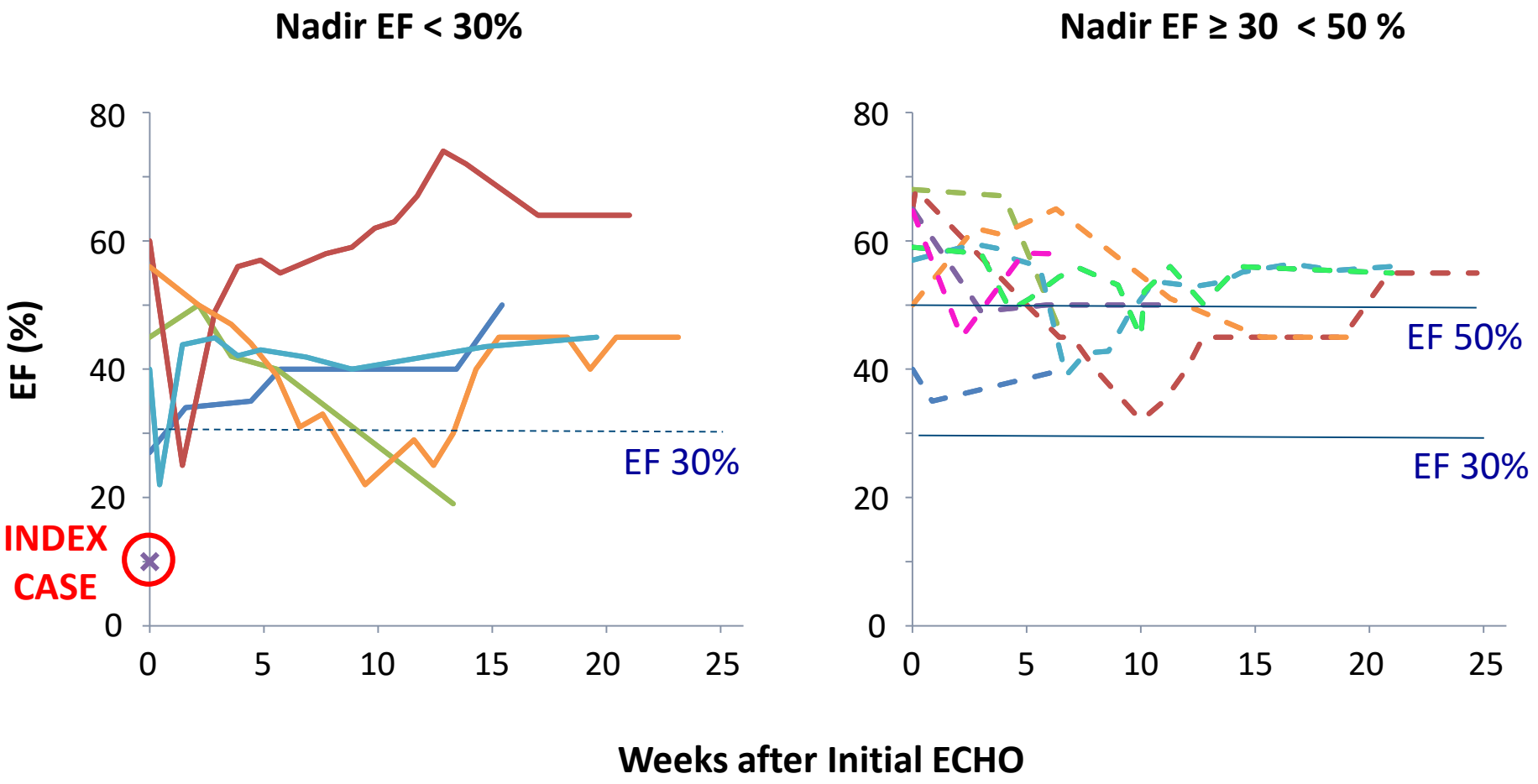


Key Findings from Dr. J Saffitz report:*

- Diffuse elongation and thinning of ventricular myocytes associated with fine interstitial fibrosis
- Consistent with severe, sub-lethal injury of cardiac myocytes (very little necrosis)
- Consistent with profound bi-ventricular dilatation and poor systolic function observed clinically
- Limited, small foci of mononuclear inflammation

*(*Chief of Pathology-Beth Israel Deaconess)*

Evidence of Recovery of Systolic Function

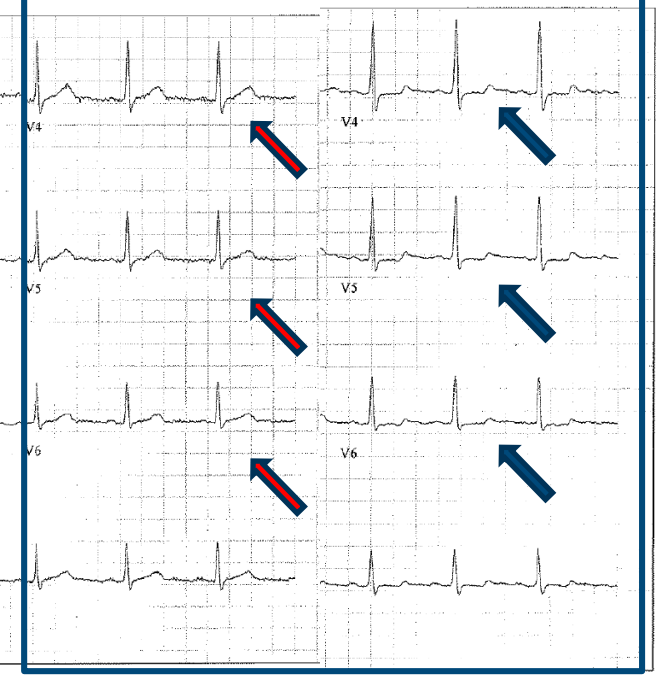


Characteristic ST-T Segment Changes

PATIENT 1

ST depression

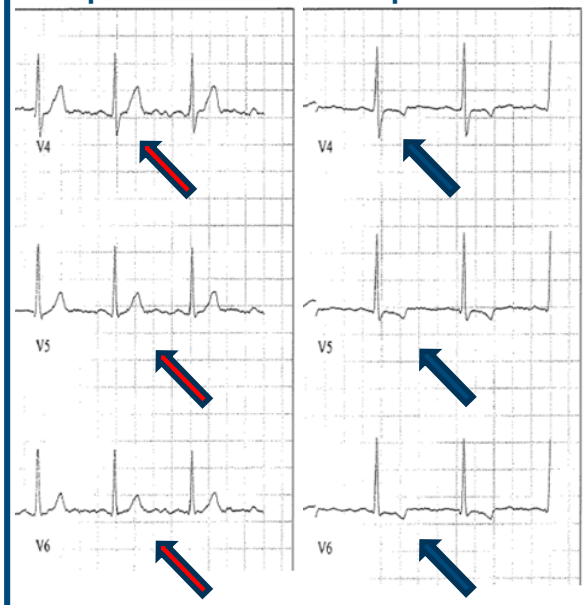
pre Week 2



PATIENT 2

T wave inversion

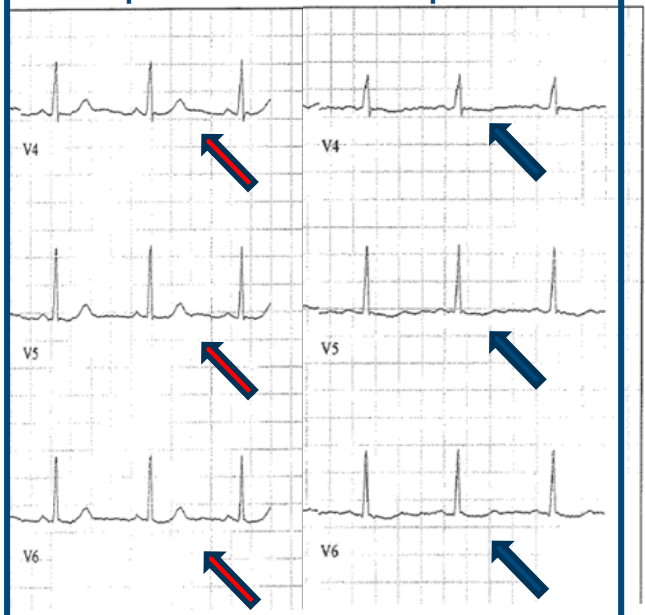
pre post



PATIENT 3

Loss of Amplitude

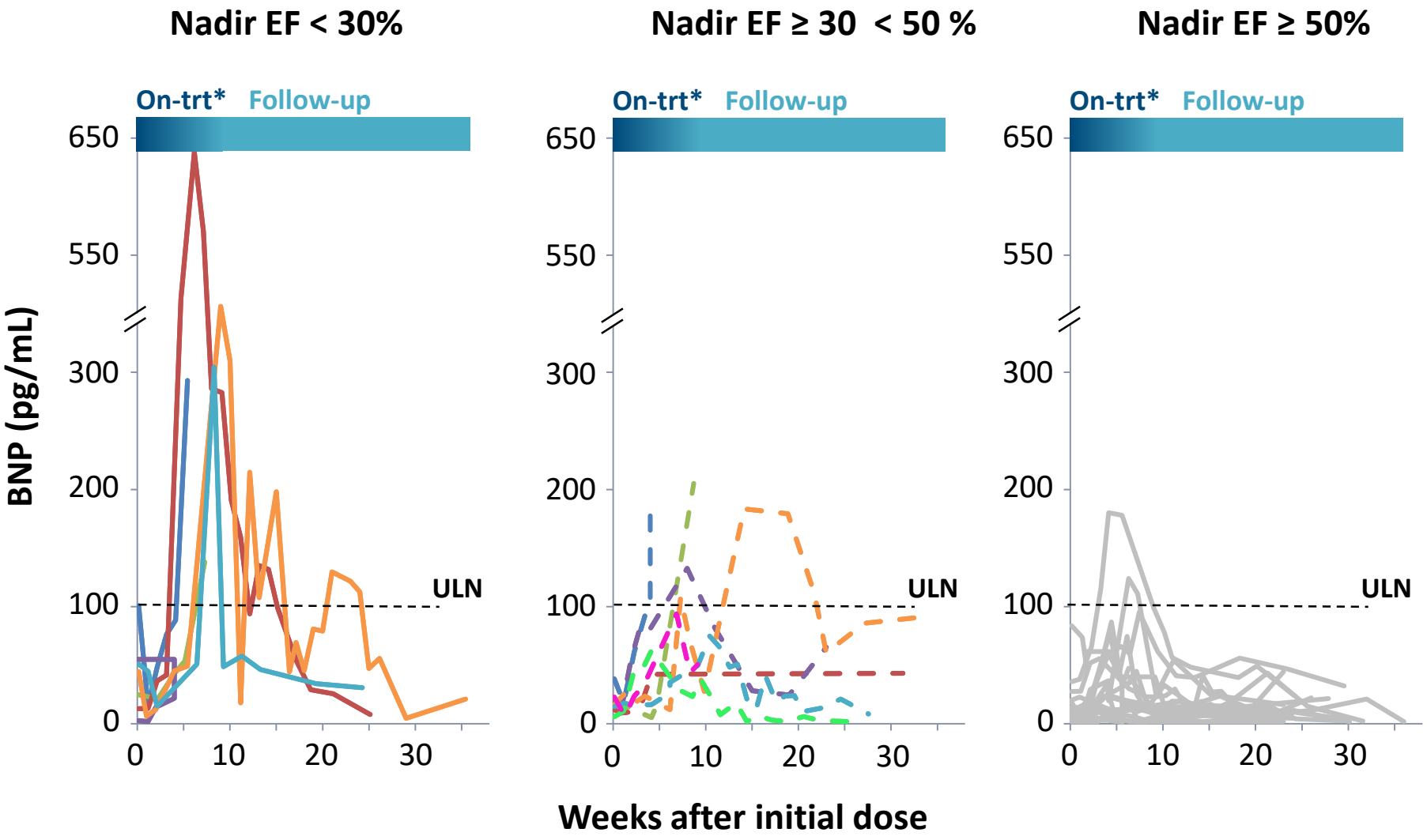
pre post



ECG: ST Segment Changes Occurred in Patients With and Without Systolic Dysfunction

	Nadir EF < 50	Nadir EF > 50
ST Depression	14% (2/14)	0% (0/20)
T wave Inversion	86% (12/14)	20% (4/20)
Loss of T Wave Amplitude	79% (11/14)	60% (12/20)

Retrospective Evaluation of BNP (tested on frozen serum)



*Patients received treatment for 1-6 weeks