Randomized, Placebo-Controlled Clinical Trial of an Aerosolized Beta-2 Agonist for Treatment of Acute Lung Injury

The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network

The members of the writing committee are Michael A. Matthay MD, Roy G. Brower, MD, Shannon Carson, MD, Ivor S. Douglas, MD, Mark Eisner, MD, Duncan Hite, MD, Steven Holets, RRT, Richard H. Kallet, RRT, MS, Kathleen D. Liu, MD, PhD, MAS, Neil MacIntyre, MD Marc Moss, MD, David Schoenfeld, PhD, Jay Steingrub, MD, and B.Taylor Thompson, MD

ONLINE DATA SUPPLEMENT

Reasons for Exclusion

Patients were excluded if more than 48 hours had elapsed since the inclusion criteria were met; they were younger than 13 years of age; they had participated in other trials involving acute lung injury within the preceding 30 days; they were pregnant; they had increased intracranial pressure; they had a history of severe neuromuscular disease, severe chronic respiratory disease, or asthma requiring inhaled beta-2 agonists; they had severe chronic liver disease, vasculitis with diffuse alveolar hemorrhage, or burns over more than 40 percent of body surface area; their body weight exceeded 1 kg per centimeter of height; they had a coexisting condition associated with an estimated 6-month mortality rate greater than 50 per cent, a moribund condition from which they were not expected to survive 24 hours, or had received a bone marrow transplant in the previous 5 years; they had an acute myocardial infarction or acute coronary syndrome within the last 30 days or severe congestive heart failure; they had a heart rate greater than 85% of predicted maximum heart rate (220 – age); they had onset of atrial fibrillation requiring anticoagulation during the current hospitalization; they had more than 5 premature ventricular contractions in a 4 hour period preceding randomization; or they were receiving high frequency ventilation. Patients were also excluded if their attending physicians were unwilling to allow enrollment or unwilling to use a mechanical ventilation strategy with a tidal volume goal of 6 ml/kg tidal volume (predicted body weight) or a fluid-conservative hemodynamic strategy.

Rationale for exclusions: Patients less than 13 years of age were excluded because delivery of albuterol may not be uniform, particularly with uncuffed endotracheal tubes. Patients with ALI for more than 48 hours were excluded to evaluate more clearly the effects of albuterol early in the course of lung injury. Exclusion with moderate to severe COPD or neuromuscular disease could have confounded the ventilator free day endpoint. Pregnancy was an exclusion because beta agonists may interfere with uterine contraction. Burns, malignancy or other irreversible conditions with 6-month survival less than 6 months, allogeneic bone marrow transplant within the last 5 years, severe chronic liver disease and

alveolar hemorrhage were excluded because the patients were thought unlikely to survive to the primary study endpoint. Patients with alveolar hemorrhage from vasculitis were excluded because the mechanism of lung injury is different from ALI and diffuse alveolar damage. Patients with contraindications to albuterol and acute myocardial infarction within 30 days were excluded because of a potential excess risk. Patients with congestive heart failure were excluded because of concerns about ventricular arrhythmias. Patients with a baseline heart rate of greater than 85% of maximal predicated heart rate were excluded, because a further increase in heart rate might have been deleterious. Patients ventilated with high frequency ventilation were excluded because dosing ofnebulized albuterol during these modes of ventilation is unreliable.

Other Secondary End Points

Other secondary endpoints included ICU-free and organ failure-free days at 28 days after randomization, VFDs and mortality in patients enrolled with a PaO_2/FiO_2 less than 200, changes from baseline in physiologic indices of lung injury including PaO_2/FiO_2, inspiratory plateau airway pressure, oxygenation index, quasistatic respiratory compliance, and the number of quadrants with pulmonary infiltrates on frontal chest radiograph.

Dose Interruptions and Adjustment for Tachycardia

Each patient's maximum allowable heart rate (MAHR) was calculated as 140 or 0.85 (220-age), whichever was lower (heart rates were monitored by continuous surface electrocardiography).

1) A scheduled study drug dose was held if sustained pretreatment heart rate exceeded the MAHR. Heart rate was then reassessed at the next scheduled treatment time.

2) If heart rate exceeded the MAHR during a nebulization treatment, the treatment was stopped, and heart rate was reassessed at the next scheduled treatment time. Because fluctuations in heart rate during critical illness may be caused by pain, general stress response, alterations in acid base status, etc, independent of albuterol treatment, the ICU teams were asked to evaluate patients whose heart rates exceeded the MAHR, to identify and treat causes of tachycardia other than study drug.

3) If heart rate subsequently decreased below the MAHR before the next scheduled dose of study drug, the next dose was give in the full dose of 5.0 mg.

4) If the heart rate increased again above the MAHR, the aerosol treatment was stopped, and subsequent study drug doses were reduced to 2.5 mg.

5) If heart rate exceeded the MAHR during or after two consecutive reduced study drug doses, study drug was held for 24 hours and restarted at the reduced dose.

6) If heart rate again increased above the MAHR, the study drug was held for another 24 hours and restarted at the reduced dose.

7) Any subsequent increases in heart rate above the MAHR resulted in discontinuation of study drug for the duration of the study.

8) If patients developed more than 5 new premature ventricular contractions (PVCs) per minute during aerosolization of the study drug, then the treatment was held. The next treatment was at the 2.5 mg reduced dose of the study drug. If there was a recurrence of the new PVCs at more than 5/minute, then the study drug was held for 24 hours and restarted at the reduced dose. Any subsequent recurrence of the new PVCs at more than 5/minute

during aerosolization resulted in permanent withdrawal of the study drug for the duration of the study.

9) In patients who develop sustained atrial arrhythmias after study entry, including new onset atrial fibrillation, atrial flutter, supraventricular tachycardia, or multifocal atrial tachycardia, the study drug was held for 24 hours. After 24 hours the study drug could be restarted at the reduced dose if the patient's physician judged that the atrial arrhythmia had been adequately treated. The drug was permanently withdrawn for any episode of ventricular tachycardia or ventricular fibrillation. Eligible patients with preexisting atrial fibrillation or multifocal atrial rhythms with a controlled ventricular response could participate in the trial. For enrolled patients with pre-existing atrial fibrillation or multifocal atrial rhythms, study drug was dosed and subsequently adjusted, held or discontinued based on changes in heart rates as described in the previous paragraphs.

Mechanical Ventilation Protocol

1. Any mode of ventilation can be used except High Frequency Ventilation**.**
2. Tidal Volume (V_T) goal is 6 ml/kg Predicted Body Weight.
3. Measure and record inspiratory plateau pressure (Pplat) according to ICU routine (at least every four hours and after changes in V_T and PEEP recommended).
4. If Pplat exceeds 30 cm H_2O, reduce V_T to 5 ml/kg and then to 4 ml/kg PBW if necessary to decrease Pplat to less than or equal to 30.
5. If V_T less than 6 ml/kg PBW and Pplat less than 25, raise V_T by 1 ml/kg PBW to a maximum of 6 ml/kg.
6. If "severe dyspnea" (more than 3 double breaths/minute or airway pressure remains at or below PEEP level during inspiration), then raise V_T to 7 or 8 ml/kg PBW if Pplat

remains below 30. If Pplat exceeds 30 on 7 or 8 ml/kg PBW, then revert to lower V_T and consider more sedation.

7. If pH less than 7.15, V_T may be raised and Pplat limit suspended (not required).
8. Oxygenation target: PaO_2 = 55-80 mm Hg or SpO_2 = 88-95%.
9. Minimum PEEP = 5 cm H_2O.
10. Adjust F_IO_2 or PEEP upward within 5 minutes of consistent measurements that are below the oxygenation target range.
11. Adjust F_IO_2 or PEEP downward within 30 minutes of consistent measurements above the oxygenation target range.
12. No specific rules for how to use PEEP and F_IO_2 (except for minimum PEEP of 5). The lower PEEP/higher FiO_2 table represents a consensus approach developed by NIH ARDS Network investigators in 1995. Clinicians can choose to use either table or to adjust PEEP and FiO2 according to a different approach.

Lower PEEP/Higher FiO_2 Treatment Group

FiO_2	.30	.40	.40	.50	.50	.60	.70	.70	.70	.80	.90	.90	.90	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18-24

Higher PEEP/Lower FiO_2 Study Group

FiO_2	.30	.30	.30	.30	.30	.40	.40	.50	.50	.50 – .80	.80	.90	1.0	1.0
PEEP	5	8	10	12	14	14	16	16	18	20	22	22	22	24

- (Levels of PEEP in these F_IO_2/PEEP scales represent levels set on the ventilator, not levels of total-PEEP, auto-PEEP, or intrinsic-PEEP.)
- No specific rules for respiratory rate. Recommended to raise respiratory rate in increments to 35/minute (maximum set rate) if pH less than 7.30.

- No specific rules regarding the inspiratory to expiratory flow ratio. Recommended that duration of Inspiration be less than or equal to duration of Expiration.
- Bicarbonate is allowed (neither encouraged nor discouraged) if pH less than or equal to 7.30.

Weaning and Extubation

Patients were assessed for the following weaning readiness criteria each day between 0600 and 1000. If a patient procedure, test, or other extenuating circumstance prevented assessment for these criteria between 0600 and 1000, then the assessment and initiation of subsequent weaning procedures could be delayed for up to six hours.

1. At least 12 hours since enrollment in the trial.
2. $F_IO_2 \leq 0.40$ and PEEP ≤ 8 cm H_2O or $FiO_2 \leq 0.50$ and PEEP ≤ 5 cm H_2O.
3. Values of both PEEP and F_IO_2 ≤ values from previous day.
4. Not receiving neuromuscular blocking agents and without clinical evidence of neuromuscular blockade.
5. Presence of inspiratory efforts. If no efforts were evident at baseline, ventilator set rate could be decreased to 50% of baseline level for up to 5 minutes to detect inspiratory efforts.
6. Systolic arterial pressure greater than or equal to 90 mm Hg without vasopressor support (≤ 5 microgram/kg/min dopamine or dobutamine was not be considered a vasopressor).

If criteria 1-6 were met, then a trial of up to 120 minutes of spontaneous breathing was initiated with $F_IO_2 \leq 0.5$ using any of the following approaches:

1. Pressure support ≤ 5 cm H_2O, PEEP ≤ 5 cm H_2O
2. CPAP ≤ 5 cm H_2O
3. T-piece
4. Tracheostomy mask

The following criteria were monitored and the spontaneous breathing trials continued if:

1. SpO_2 ≥ 90% or PaO_2 ≥ 60 mmHg.
2. Mean spontaneous tidal volume ≥ 4 ml/kg PBW, if measured.
3. Respiratory rate ≤ 35/min.
4. pH ≥ 7.30, if measured.
5. No respiratory distress (2 or more of the following):
    a. Heart rate greater than or equal to 120% of the 0600 rate (less than or equal to 5 min at greater than 120% may be tolerated).
    b. Marked use of accessory muscles.
    c. Abdominal paradox.
    d. Diaphoresis.
    e. Marked subjective dyspnea.

If any of goals a, b, or c were not met, the previous ventilator settings were restored. Alternatively, patients could receive Pressure Support ventilation with greater than or equal to 10 cm H_2O of pressure support and with positive end-expiratory pressure and F_IO_2 equal to the previous settings.

The clinical team could change mode of support during spontaneous breathing (PS = 5, CPAP, tracheostomy mask, or T-piece) at any time.

Decision to remove ventilatory support

For intubated patients, if tolerance criteria for spontaneous breathing trial (1-5 above) were met for at least 30 minutes, the clinical team could decide to extubate. However, the spontaneous breathing trial could continue for up to 120 minutes if tolerance remained in question. If any of criteria 1-5 were not met during unassisted breathing (or 120 minutes had passed without clear tolerance), then the ventilator settings that were in use before the attempt to wean were restored and the patient was reassessed for weaning the following day.

Completion of ventilator procedures

Patients were considered to have completed the study ventilator procedures if any of the following conditions occurred:

1. Death
2. Hospital discharge.
3. Alive 28 days after enrollment.

If a patient required positive pressure ventilation after a period of unassisted breathing, the study ventilator procedures were resumed unless the patient was discharged from the hospital or greater than 28 days had elapsed since enrollment.

Definition of Unassisted Breathing

1. Extubated with face mask, nasal prong oxygen, or room air, OR
2. T-tube breathing, OR
3. Tracheostomy mask breathing, OR
4. CPAP less than or equal to 5 cm H_2O without pressure support or IMV assistance.

Conservative Fluid Management Algorithm

This protocol should be initiated within four hours of randomization in enrolled patients and continued until unassisted breathing or study day seven, whichever occurs first.

1. Discontinue maintenance fluids.
2. Continue medications and nutrition.
3. Manage electrolytes and blood products per usual practice.
4. For shock, use any combination of fluid boluses[#] and vasopressor(s) to achieve MAP ≥ 60 mmHg as quickly as possible. Wean vasopressors as quickly as tolerated beginning four hours after blood pressure has stabilized.
5. Withhold diuretic therapy in renal failure**.

<table>
<tr><th rowspan="2">CVP
(recommended)</th><th rowspan="2">PAOP
(optional)</th><th colspan="2">MAP ≥ 60 mm Hg AND off vasopressors for ≥ 12 hours</th></tr>
<tr><th>Average urine output < 0.5 ml/kg/hr</th><th>Average urine output ≥ 0.5 ml/kg/hr</th></tr>
<tr><td>> 8</td><td>> 12</td><td>Furosemide*
Reassess in 1 hour</td><td rowspan="2">Furosemide*
Reassess in 4 hours</td></tr>
<tr><td>4-8</td><td>8-12</td><td rowspan="2">Give fluid bolus as fast as possible[#]
Reassess in 1 hour</td></tr>
<tr><td>< 4</td><td>< 8</td><td>No intervention
Reassess in 4 hours</td></tr>
</table>

[#] Recommended fluid bolus= 15 mL / kg crystalloid (round to nearest 250 mL) or 1 Unit packed red cells or 25 grams albumin

* Recommended Furosemide dosing: Begin with 20 mg bolus or 3 mg / hr infusion or last known effective dose. Double each subsequent dose until goal achieved (oliguria reversal or

intravascular pressure target) or maximum infusion rate of 24 mg / hr or 160 mg bolus reached. Do not exceed 620 mg / day. Also, if patient has heart failure, consider treatment with dobutamine.

**Renal failure: dialysis dependence, OR oliguria with serum creatinine greater than 3 mEq/dl, or oliguria with creatinine 0-3 mEq/dl with urinary indices indicative of acute renal failure.

Fluid management continued until day seven or the day of unassisted breathing, whichever occurred first.

Aerosolized Drug Delivery Protocol

All ventilator circuits were required to use active humidification during the study. Heat-moisture exchangers were not allowed so as to prevent loss of aerosolized drug delivery because of impaction and deposition of aerosol on the filter. To the inspiratory limb of the ventilator circuit was added an 18 cm reservoir of aerosol tubing and an Airlife valved T-adapter (Cardinal Health, MacGaw, IL) that allowed the nebulizer to be placed and removed without breaking the ventilator circuit. For sites that used heated-wire circuits, an additional temperature probe adapter was provided so that the temperature could continue to be controlled at the circuit Y-adapter.

To enhance study drug delivery the following guidelines were included in the protocol. First, prior to administering the study drug, clinicians were to suction the artificial airway if there were secretions. Second, as a dry ventilator circuit stabilizes aerosol particles (causing less drug loss from impaction against the artificial airway), the humidifier was turned-off prior

to beginning aerosol treatment and turned-on after completion of therapy. Third, the oxygen flow meter was adjusted to 8 L/min to maximize drug delivery efficiency. However, if the ventilator's high-pressure limit alarm sounded frequently or the patient was observed to be unable to trigger assisted breaths, then the flow rate of the oxygen flow meter was decreased in steps of 1 L/min to a minimum of 5 L/min. Fourth, because high peak inspiratory flow rates (> 60 L/min) increase drug loss by enhanced impaction on the ET tube, clinicians were instructed to decrease the peak inspiratory flow rate to a target of 30 L/min (square-wave flow pattern) or 55 L/min (decelerating flow pattern) during nebulization to increase drug delivery. To address this problem the inspiratory-to-expiratory ratio was increased to approximately 1:1. When pressure-regulated modes were used, a moderate pressure rise-time of approximately 0.5 sec was recommended to prevent high peak flow rates. If patient-ventilator asynchrony was noted during the treatment, then the inspiratory-to-expiratory ratio or pressure-rise time were adjusted to the clinical response.

In addition, the inspiratory circuit and support arm were adjusted to secure the nebulizer in an upright position to prevent inadvertent drug spillage into the circuit during nebulization. A spring loaded T adapter was utilized to maintain circuit integrity and prevent alveolar derecruitment. For safety reasons, tidal volume was not reduced during the treatments.

Laboratory Testing of Jet Nebulizers.

The jet nebulizer chosen for this study, the Airlife Misty Max (Cardinal Health, MacGaw, IL), was selected based upon its performance characteristics tested in an aerosol laboratory. Aerosol particle size was assessed by measuring the volumetric median diameter (VMD), whereas particle uniformity was assessed by measuring the geometric standard deviation (GSD). Particle sizing was assessed using the laser defraction method which

measures particle size a few centimeters distal from the aerosol generator. Three of the jet nebulizers were tested at the drive flow rate specified by the manufacturer (8 L/min). Initial tests were conducted with normal saline to determine the best performers as saline typically has the same nebulization time as albuterol. Then, tests were repeated using a 0.5% solution of albuterol sulfate.

The Airlife Misty Max (Cardinal Health, MacGaw, IL) had a VMD of 3.7 microns, which is well within the respirable range (< 5.5 microns). This translates approximately into a Mass-Median Aerodynamic Diameter of 3.1 microns (as determined with an Anderson Cascade Impactor at 28.3 L/min). Likewise, uniformity of particle size distribution was good with a GSD of 2.2 microns. In addition, the MistyMax nebulizer generated an acceptable aerosol output rate of 0.30 mL/min.

Efficacy and Futility Stopping Boundaries

The trial was designed to enroll a maximum of 1,000 patients. Interim analyses of the primary outcome, ventilator-free days, were planned after enrollment of 100, 250, 500, and 750 patients. The trial could stop at an interim analysis for either efficacy or futility. The trial could stop for efficacy if there was a difference in ventilator-free days that favored the albuterol study group by a substantial amount, providing convincing evidence that albuterol treatment was superior to placebo treatment. To stop the trial for efficacy after enrollment of 100 patients would have required a 9.5 ventilator-free days difference favoring the albuterol group (albuterol ventilator-free days minus placebo ventilator-free days). To stop the trial for efficacy after enrollment of 250, 500, and 750 patients would have required differences in ventilator-free days of 3.8, 1.9, and 1.3 days, respectively.

The trial was also designed to stop for futility if the probability that we could demonstrate efficacy was very low, even if our original estimation of treatment effect (2.25

ventilator-free days) was correct and we continued the trial to the maximum planned enrollment of 1,000 days. The trial could not stop for futility after enrollment of just 100 patients. The trial could stop for futility after enrollment of 250 patients if the difference in ventilator-free days was $\leq$ -0.50 days (at least 0.50 days favoring the placebo group). It could stop for futility after enrollment of 500 and 750 patients if the difference in ventilator-free days was < 0.14 and < 0.35 days, respectively (favoring the albuterol group).

The differences in ventilator-free days required to stop for efficacy and futility are different (asymmetric stopping boundaries) because the conditions required to stop for efficacy and futility are different. The condition required to stop for efficacy was convincing evidence of greater ventilator-free days in the albuterol group. In contrast, the condition required to stop for futility is that the probability of demonstrating efficacy if we continued the trial was small.

Number of patients	P-value Efficacy 2-sided	Difference Efficacy	Difference Futility	Type I Error Spending 1-sided	Type II Error Spending	Prob Stop futility	Prob Stop efficacy	Confidence interval when no difference
100	1.5 E-6	9.5		7.6 E-11	0	0	5 E-8	9.3-17.6
250	5 E-5	3.8	-0.50	2.56 E-5	0.0128	0.30	0.009	2.8-8.0
500	0.0042	1.9	0.14	0.0021	0.0232	0.31	0.31	.8-4.5
750	0.0194	1.3	0.35	0.0104	0.0287	0.17	0.41	.3-3.2
1000	0.0429	0.95	0.46	0.0250	0.0923	0.09	0.18	0.0-2.6

Statistical Method Details

A logistic model was fit to the data using treatment and the seven covariates as predictor variables. The estimates from the logistic model were then used to calculate two predicted mortalities for each patient: one assuming albuterol treatment and the other assuming placebo treatment. The averages of these predicted mortalities give the adjusted mortality rates for the two treatment arms.

Tables for the Supplement

Table S1. Baseline and day 3 plasma levels of IL-6 and IL-8

Log IL-6 Levels

	Albuterol		Placebo		
Study Day	Mean ± SD	N	Mean ± SD	N	P Value
0	2.3 ± 0.7	144	2.2 ± 0.7	117	0.973
3	1.9 ± 0.6	127	1.8 ± 0.7	110	0.366

Log IL-8 Levels

	Albuterol		Placebo		
Study Day	Mean ± SD	N	Mean ± SD	N	P Value
0	1.9 ± 0.6	144	1.8 ± 0.6	117	0.407
3	1.7 ± 0.5	127	1.7 ± 0.5	110	0.432

IL-6 and IL-8 levels were normalized using the log (base 10) transformation. Wilcoxon's test was used to compare mean log-transformed cytokine levels on days 0 and 3

Table S2. Epinephrine Levels by Treatment Group

	Albuterol (n= 49)	Placebo (n=39)	P-value[1]
Epinephrine, median (IQR)			
Baseline	71 (42-106)	39 (31-94)	0.02
Day 1	53 (39-102)	53 (29-81)	0.38

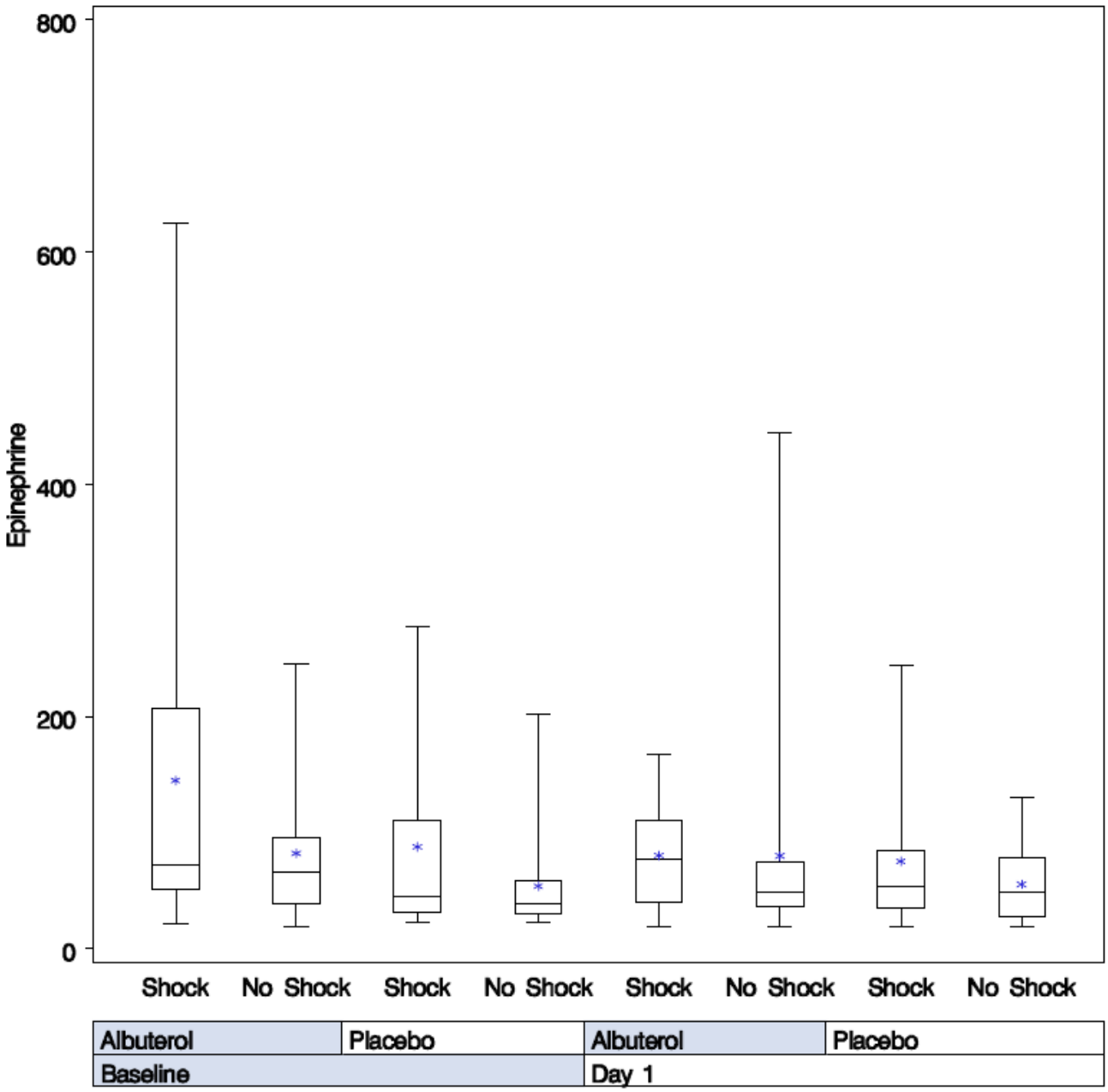
[1] P-values were given by the Wilcoxon Rank Sum test. There was no difference in the change of Epinephrine levels from baseline to day 1 by the treatment using analysis of covariance (p=0.72, Epinephrine levels were rank transformed because of non-normal distribution).

Table S3. On Study Dosing: Percent of Patients Completing Every Dose as Full Dose of ALTA Study Drug

Day	DRUG	PLACEBO	Total	Pvalue
0	88.4% (147)	89.4% (123)	88.9% (270)	0.80
1	77.7% (148)	85.0% (127)	81.1% (275)	0.12
2	70.6% (143)	82.9% (123)	76.3% (266)	0.02
3	79.2% (125)	75.2% (113)	77.3% (238)	0.46
4	80.6% (103)	78.4% (97)	79.5% (200)	0.70
5	77.7% (94)	78.7% (89)	78.1% (183)	0.87
6	77.5% (80)	79.2% (77)	78.3% (157)	0.79
7	78.6% (70)	66.7% (60)	73.1% (130)	0.13
8	69.5% (59)	61.7% (47)	66.0% (106)	0.40
9	64.6% (48)	70.7% (41)	67.4% (89)	0.54
10	69.0% (42)	69.0% (29)	69.0% (71)	0.99

Figure Legend for Figure S1. Box plots of baseline and day 1 plasma levels of epinephrine (in picograms per ml) are shown for subjects with and without shock at baseline for the first 92 subjects. Three subjects receiving intravenous epinephrine at baseline were excluded. Upper and lower margins of the boxes represent the 25^{th} and 75^{th} quartiles. The bars in the boxes are medians.

Figure S1


800
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