CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA209360/S0001
Drug Name:	(b) (4) (angiotensin II) Injection for Intravenous Infusion (LJPC-501)
Indication(s):	Treatment of hypotension in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy
Applicant:	La Jolla Pharmaceutical Company
Date(s):	Date of Document: June 29, 2017 PDUFA Due Date: March 01, 2018
Review Priority:	Priority
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Ququan Liu, M.D., M.S.
Concurring Reviewers:	Hsien-Ming James Hung, Ph.D.
Medical Division:	Biometrics I, HFD-710
Clinical Team:	Fortunato Senatore, M.D.
Project Manager:	Sabry Soukehal
Keywords:	LJPC-501, Hypotension, Distributive/Vasopressor Therapy

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The study seems to support that LJPC-501 is superior in the treatment of catecholamine-resistant hypotension (CRH) compared to the placebo in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy.

1.2 Brief Overview of Clinical Studies

This NDA is intended to obtain approval of an indication for the treatment of CRH based on a phase 3, placebo-controlled, randomized, double-blind, multicenter study of LJPC-501 in patients with CRH. The primary objective of this study was to evaluate the effect of LJPC-501 infusion on mean arterial pressure (MAP). The primary efficacy endpoint was clinical response at 3 hours as defined by achieving a MAP of at least 75 mmHg or 10 mmHg above baseline without increasing other vasopressor doses.

1.3 Statistical Issues and Findings

Overall the efficacy of LJPC-501 in increasing MAP seems evident. The primary efficacy endpoint of percent responders achieving the target MAP at hour 3 was statistically significantly higher in the LJPC-501 group compared to the placebo group (69.9% and 23.4%, for LJPC-501 and placebo, respectively; $p<0.0001$). The efficacy was also consistent trending in favor of LJPC-501across the subgroups of age, gender, geographic regions and selected special populations with underlining disease characteristics.

2. INTRODUCTION

2.1 Overview

LJPC-501 was developed for the treatment of CRH. CRH describes the clinical state of distributive shock which fails to respond to fluid and available vasopressor therapy. The catecholamine norepinephrine, dopamine, and epinephrine are recommended as first-line treatment for hypotensive shock. Vasopressin is also used to treat severe hypotension and may reduce norepinephrine requirements. As with other vasopressors, LJPC-501 is intended for use in the intensive care unit (ICU) and expected to be used in combination with standard-of-care fluid resuscitation and vasopressors. Reduction in the doses of concomitant vasopressors is hypothesized to improve safety and potentially reduce mortality in patients with hypotensive shock.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of \\CDSESUB1\evsprod\NDA209360\0001\ the Center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

A consistent result of the primary efficacy analysis can be generated from both raw and derived data.

3.2 Evaluation of Efficacy

3.2.1 Primary Study Objective

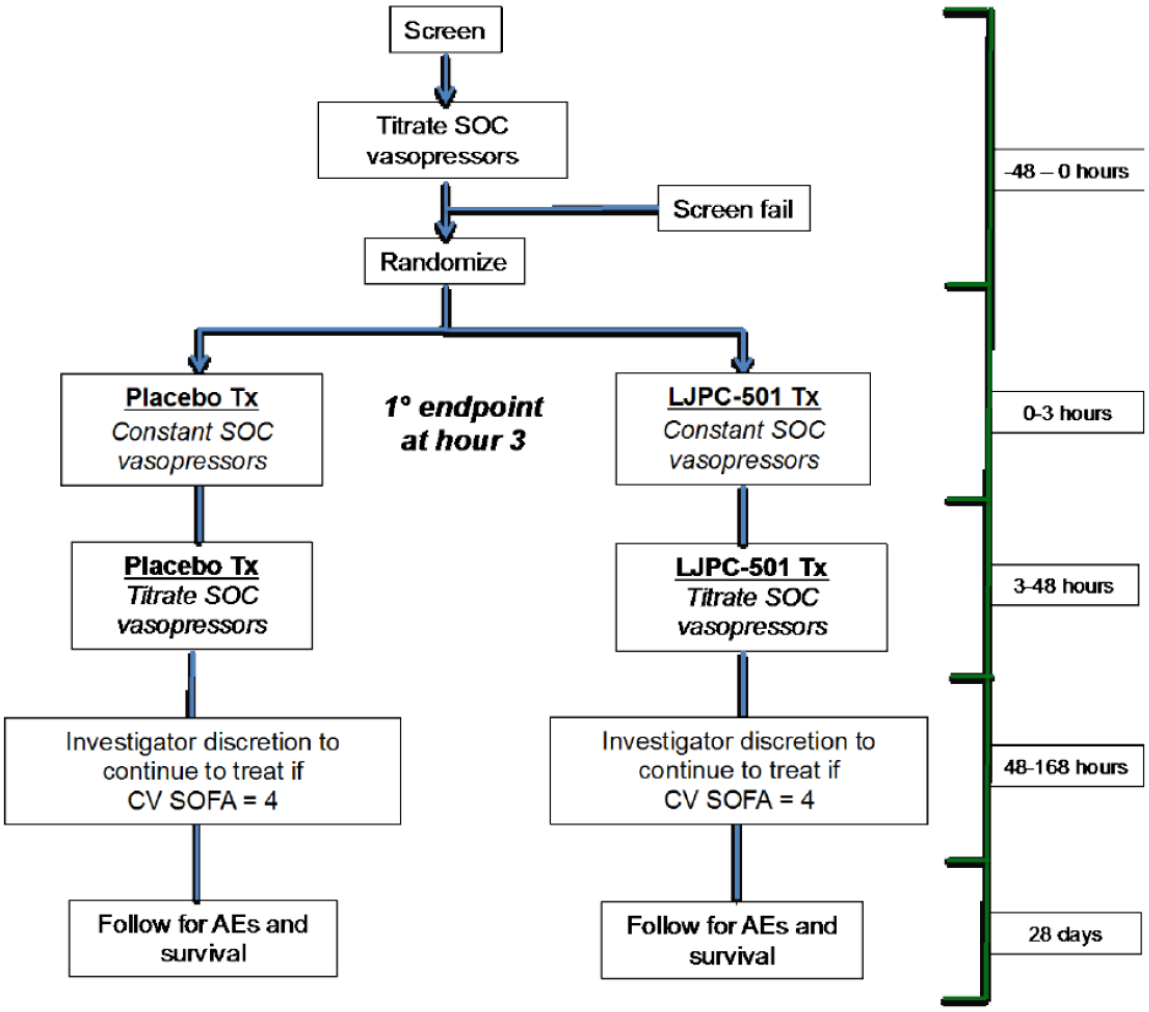
The primary objective of the study (LJ501-CRH01) was to evaluate the effect of LJPC-501 infusion on MAP in patients with CRH.

3.2.2 Study Design

LJ501-CRH01 was a multicenter, randomized, double-blind, placebo-controlled, parallel 2-arm study that enrolled adult patients with CRH who were hospitalized in an intensive care setting. The study design was described in Figure 1.

Sample size of 315 patients was based on a hypothesized response rate in the primary efficacy endpoint of 40% in the placebo arm and 60% in the LJPC-501 arm, a ratio of 1:1 for randomization, a two-by-two Chi-square test with a two-sided alpha of 0.05. This sample size will have a 90% power to demonstrate superiority of LJPC-501 over placebo.

Figure 1. Study Flow Chart



Abbreviations: AE = adverse event; CV = cardiovascular; SOC = standard-of-care; SOFA = sequential organ failure assessment; Tx = treatment.

(Source: The sponsor's Figure 1)

3.2.3 Efficacy Measures and Analyses

1) Primary Efficacy Endpoint: Targeted MAP at Hour 3. Targeted MAP was defined as MAP ≥75 mmHg or ≥10 mmHg above from Baseline at Hour 3 without increasing in non-study drug vasopressors (total norepinephrine equivalent dose).

2) Secondary Efficacy Endpoints: Change in Cardiovascular (CV) Sequential Organ Failure Assessment (SOFA) score and Total SOFA scores from screening to Hour 48.

3) Statistical Analysis Methodology:

- Primary efficacy endpoint (targeted MAP at Hour 3): A logistic regression was used for the primary endpoint analysis adjusted by fixed covariates of baseline MAP (<65 mmHg vs ≥65 mmHg), Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score,

vasopressin use over the 6 hours prior to randomization (yes vs no), and average norepinephrine equivalent dose over the 6 hours prior to randomization using modified intent-to-treat (mITT, all patients who received study drug) population.

- Secondary efficacy endpoints:
  - Change in CV SOFA score: The stratified van Elteren stratified Wilcoxon rank test with strata was used for the data analysis using mITT population.
  - Change in Total SOFA scores: An adjusted general linear model including all randomization strata was used for the data analysis using mITT population.

- Multiplicity: Hierarchical testing strategy was applied to preserve Type 1 error across the primary and secondary efficacy endpoints in the following order: significant treatment effect for the primary efficacy hypothesis; change in CV SOFA at Hour 48; and change in Total SOFA scores at Hour 48.

- Handling missing data:
  - Missing primary and secondary endpoints due to death: A failure was assigned to missing primary endpoint. A CV SOFA score of 4 and a Total SOFA scores of 24, the highest scores for the respective endpoints were assigned to missing SOFA scores.
  - Missing primary and secondary endpoints for reasons other than death: In the mITT population, the last observed MAP value was carried forward as a primary imputation method. Multiple imputation was used as a sensitivity analysis for the primary endpoint in the mITT analysis population

- Interim analysis: An interim analysis was conducted after data for 150 evaluable patients through Day 28 were collected. Blinded data using data pooled across the 2 treatment arms were reviewed by the open-session participants including La Jolla representatives. Unblinded data analyses including tables, figures, and listings were provided by an independent statistician to the DSMB for review of efficacy and safety according to the DSMB Charter.

3.2.4 Patient Disposition, Demographic and Baseline Characteristics

1) Patient Disposition

A total of 344 subjects were enrolled. 321 subjects were included in mITT population and approximately 87% of subjects were included in the PP population (Table 1).

Table 1 Analysis Population

	Number (Percentage) of Enrolled Patients		
Population	**Placebo**	**LJPC-501**	**All Patients**
All Enrolled, n (%)	172 (100%)	172 (100%)	344 (100%)
Intent-to-treat (ITT), n (%)	172 (100%)	172 (100%)	344 (100%)
Modified Intent-to-treat (mITT), n (%)	158 (92.4%)	163 (94.2%)	321 (93.3%)
Per-Protocol (PP) Population, n (%)	149 (86.6%)	150 (87.2%)	299 (86.9%)
Safety, n (%)	158 (92.4%)	163 (94.2%)	321 (93.3%)

(Source: Sponsor's Table 13, confirmed by the reviewer's analysis)

2) Patient Demographic and Baseline Characteristics

The demographic, baseline characteristics and baseline disease characteristics were similar in both treatment arms. The mean age was 62 years, and 61% of patients were males (Tables 2&3).

Table 2 Patient Demographic and Baseline Characteristics, mITT

Characteristic	**Placebo (N = 158)**	**LJPC-501 (N = 163)**	**All Patients (N = 321)**
Age, n (%)			
< 65 years	77 (48.7%)	90 (55.2%)	167 (52.0%)
≥ 65 years	81 (51.3%)	73 (44.8%)	154 (48.0%)
< 75 years	116 (73.4%)	122 (74.8%)	238 (74.1%)
≥ 75 years	42 (26.6%)	41 (25.2%)	83 (25.9%)
Mean (SD), years	62.5 (15.16)	62.1 (15.59)	62.3 (15.36)
Median (range), years	65 (22 – 89)	63 (22 – 89)	64 (22 – 89)
Gender, n (%)			
Male	103 (65.2%)	92 (56.4%)	195 (60.7%)
Female	55 (34.8%)	71 (43.6%)	126 (39.3%)
Ethnicity, n (%)			
Hispanic or Latino	7 (4.4%)	10 (6.1%)	17 (5.3%)
Not Hispanic or Latino	151 (95.6%)	153 (93.9%)	304 (94.7%)
Race, n (%)			
White	122 (77.2%)	135 (82.8%)	257 (80.1%)
Black or African American	19 (12.0%)	14 (8.6%)	33 (10.3%)
Asian	8 (5.1%)	5 (3.1%)	13 (4.0%)
Native Hawaiian/Other Pacific Islander	1 (0.6%)	0	1 (0.3%)
American Indian/Alaska Native	0	1 (0.6%)	1 (0.3%)
Other	8 (5.1%)	8 (4.9%)	16 (5.0%)
Geographic region, n (%)			
US/Canada	120 (75.9%)	116 (71.2%)	236 (73.5%)
Europe	14 (8.9%)	19 (11.7%)	33 (10.3%)
Australia/New Zealand	24 (15.2%)	28 (17.2%)	52 (16.2%)
Body mass index at baseline, kg/m^2	(N = 155)	(N = 161)	(N = 316)
< 30	84 (54.2%)	92 (57.1%)	176 (55.7%)
≥ 30	71 (45.8%)	69 (42.9%)	140 (44.3%)

(Source: The sponsor's Table 14, confirmed by the reviewer's analysis)

Table 3 Disease Characteristics at Baseline, mITT

Characteristic	Placebo (N = 158)	LJPC-501 (N = 163)	All Patients (N = 321)
Screening MAP (mmHg)			
< 65	55 (34.8%)	67 (41.1%)	122 (38.0%)
≥ 65	103 (65.2%)	96 (58.9%)	199 (62.0%)
Mean (SD)	65.4 (3.83)	65.5 (3.48)	65.5 (3.65)
Median (range)	66.5 (53.5 - 74.3)	66.0 (55.8 – 73.7)	66.3 (53.5 – 74.3)
Baseline MAP (mmHg)			
< 65	50 (31.6%)	52 (31.9%)	102 (31.8%)
≥ 65	108 (68.4%)	111 (68.1%)	219 (68.2%)
Mean (SD)	65.4 (5.57)	66.4 (5.25)	65.9 (5.42)
Median (range)	66.3 (43.3 – 80.0)	66.3 (47.3 – 92.3)	66.3 (43.3 – 92.3)
Baseline APACHE II			
≤ 30	93 (58.9%)	105 (64.4%)	198 (61.7%)
31-40	54 (34.2%)	50 (30.7%)	104 (32.4%)
≥ 41	11 (7.0%)	8 (4.9%)	19 (5.9%)
Mean (SD)	28.7 (8.29)	27.3 (8.42)	28.0 (8.37)
Median (range)	29.0 (12 – 51)	27.0 (9 – 54)	28.0 (9 – 54)
Baseline albumin (g/dL)	(N = 156)	(N = 154)	(N = 310)
< 2.5 g/dL	89 (57.1%)	103 (66.9%)	192 (61.9%)
≥ 2.5 g/dL	67 (42.9%)	51 (33.1%)	118 (38.1%)
Mean (SD)	2.4 (0.56)	2.3 (0.66)	2.3 (0.61)
Median (range)	2.4 (1.1 – 3.8)	2.2 (1.0 – 4.7)	2.3 (1.0 – 4.7)
ScvO2 (%)	(N = 117)	(N = 120)	(N = 237)
Mean (SD)	77.2 (8.60)	77.6 (8.92)	77.4 (8.75)
Median (range)	77.0 (35.0 – 96.5)	76.9 (44.9 – 99.0)	77.0 (35.0 – 99.0)
Central venous pressure (mmHg)	(N = 123)	(N = 126)	(N = 249)
Mean (SD)	12.8 (4.67)	13.7 (5.05)	13.3 (4.88)
Median (range)	12.0 (1 – 28)	13.0 (5 – 35)	12.0 (1 – 35)
Cardiac index (L/min/m2)	(N = 73)	(N = 69)	(N = 142)
Mean (SD)	3.4 (1.01)	3.3 (0.93)	3.4 (0.97)
Median (range)	3.2 (2.4 – 6.6)	3.0 (2.1 – 6.4)	3.1 (2.1 – 6.6)
Baseline MELD score			

Mean (SD)	21.9 (7.28)	20.4 (7.46)	21.1 (7.40)
Median (range)	23.0 (4 – 41)	21.0 (6 – 36)	22.0 (4 – 41)
< 30	138 (87.3%)	145 (89.0%)	283 (88.2%)
≥ 30	20 (12.7%)	18 (11.0%)	38 (11.8%)
Exposure to ACE inhibitors	15 (9.5%)	15 (9.2%)	30 (9.3%)
Exposure to ARBs	11 (7.0%)	11 (6.7%)	22 (6.9%)
Chest x-ray finding of ARDs	51 (32.3%)	40 (24.7%)	91 (28.4%)
Medical history of sepsis	132 (83.5%)	127 (77.9%)	259 (80.7%)
Cause of distributive shock			
Sepsis	132 (83.5%)	127 (77.9%)	259 (80.7%)
Other/potentially sepsis	11 (7.0%)	20 (12.3%)	31 (9.7%)
Vasoplegia	9 (5.7%)	10 (6.1%)	19 (5.9%)
Pancreatitis	2 (1.3%)	0	2 (0.6%)
Other	4 (2.5%)	6 (3.7%)	10 (3.1%)
Vasopressin use during 6 h prior to randomization	111 (70.3%)	113 (69.3%)	224 (69.8%)
Average NED dose during 6 h prior to randomization (μg/kg/min)			
Mean (SD)	0.53 (0.423)	0.49 (0.340)	0.51 (0.383)
Median (range)	0.41 (0.10 – 3.02)	0.40 (0.09 – 2.97)	0.40 (0.09 – 3.02)
Number of vasopressors at Baseline			
Mean (SD)	2.0 (0.74)	1.9 (0.80)	2.0 (0.77)
Median (range)	2 (1-4)	2 (1-4)	2 (1-4)
Baseline NED dose (μg/kg/min)			
Mean (SD)	0.48 (0.445)	0.45 (0.353)	0.46 (0.400)
Median (range)	0.34 (0.05 – 3.80)	0.33 (0.08 – 2.58)	0.34 (0.05 – 3.80)
< 0.2 μg/kg/min	15 (9.5%)	20 (12.3%)	35 (10.9%)
≥ 0.2 – < 0.35 μg/kg/min	68 (43.0%)	63 (38.7%)	131 (40.8%)
≥ 0.35 – < 0.50 μg /kg/min	27 (17.1%)	34 (20.9%)	61 (19.0%)
≥ 0.50 μg /kg/min	48 (30.4%)	46 (28.2%)	94 (29.3%)

(Source: The sponsor's Table 15, confirmed by the reviewer's analysis)

3.2.5 Sponsor's Primary Efficacy Results

The percent of responders was statistically significantly higher in the LJPC-501 group compared to the placebo group (70% vs. 23% for LJPC-501 and placebo, respectively; P<0.0001, Table 4). There was no missing MAP value for the primary analysis.

Table 4 Primary Efficacy Analysis of MAP at Hour 3

Analysis	Placebo N = 158	LJPC-501 N = 163	Total N = 321
Number responding (n)	37	114	151
Percent responding	23.4%	69.9%	47.0%
95%[a]	17.1% - 30.8%	62.3% - 76.9%	41.5% - 52.7%
Primary analysis Independent variable[b]:	**Odds Ratio (95% CI)**		**p value**
Treatment, LJPC-501	7.95 (4.76 - 13.3)		2.54E-15
Baseline MAP, < 65 mmHg	0.49 (0.28 - 0.86)		0.0122
Baseline APACHE II score	1.00 (0.97 - 1.03)		0.9218
Vasopressin during 6 h prior to randomization	0.93 (0.53 - 1.62)		0.7938
Average NED in 6 h prior to randomization	0.60 (0.29 - 1.26)		0.1803

Abbreviations: APACHE = Acute Physiologic Assessment and Chronic Health Evaluation; MAP = mean arterial pressure; mITT = modified intent-to-treat; NED = norepinephrine-equivalent dose.
[a] Exact binomial 95%
[b] Chi-square test from logistic regression model including LJPC-501 treatment (compared to placebo) adjusted by baseline MAP (<65 mmHg / ≥ 65 mmHg), baseline APACHE II score, vasopressin use 6 hours prior to randomization (yes / no), and mean norepinephrine-equivalent dose over the 6 hours prior to randomization.

(Source: The sponsor's Table 26, confirmed by the reviewer's analysis)

3.2.6 Sponsor's Secondary Efficacy Results

1) CV SOFA Score:
There was a statistically significant reduction on CV SOFA score at Hour 48 in the LJPC-501 group compared to the placebo group (means of -1.75 and -1.28 for LJPC-501 and placebo, respectively; P=0.0129, Table 5).

Table 5 Secondary Efficacy Analysis of CV SOFA Score at Hour 48, mITT

Timepoint Statistic	Placebo N = 158	LJPC-501 N = 163	Total N = 321
Day 2, Hour 48	(N = 158)	(N = 163)	(N = 321)
Mean (SD)	2.72 (1.654)	2.25 (1.771)	2.48 (1.729)
Median (range)	4 (0 - 4)	3 (0 - 4)	3 (0 - 4)
Score distribution	(N = 158)	(N = 163)	(N = 321)
0	36 (22.8%)	54 (33.1%)	90 (28.0%)
1	9 (5.7%)	12 (7.4%)	21 (6.5%)
2	0	2 (1.2%)	2 (0.6%)
3	31 (19.6%)	30 (18.4%)	61 (19.0%)
4	51 (32.3%)	44 (27.0%)	95 (29.6%)
4 (last observation carried forward)	2 (1.3%)	0	2 (0.6%)
4 (worst case, death)	29 (18.4%)	21 (12.9%)	50 (15.6%)

Change from Screening to Hour 48			
Mean (SD)	−1.28 (1.654)	−1.75 (1.771)	−1.52 (1.729)
Median (Range)	0 (−4 – 0)	−1 (−4 – 0)	−1 (−4 – 0)
p value (van Elteren Wilcoxon)	0.0129		

Source: Table 14.2.2.1.1
Note: All patients had a CV SOFA score of 4 (highest risk) at Screening based on inclusion/exclusion criteria. For patients missing a 48-hour assessment, the last observation was carried forward. In the event of death prior to the 48-hour assessment, the patient was assigned a CV SOFA score of 4. The van Elteren Wilcoxon rank test compared LJPC-501 to placebo adjusting for Baseline MAP, Screening APACHE II score, and Screening SOFA score.
Abbreviations: APACHE II = Acute Physiologic Assessment and Chronic Health Evaluation II; MAP = mean arterial pressure; mITT = modified intent-to-treat; SOFA = sequential organ failure assessment

(Source: The sponsor's Table 34, confirmed by the reviewer's analysis)

2) Total SOFA Scores:

There was no difference on the reduction of total SOFA scores between the two groups (means of 1.05 and 1.04 for LJPC-501 and placebo, respectively; P=0.4901, Table 6).

Table 6 Secondary Efficacy Analysis of Total SOFA Scores at Hour 48, mITT

Timepoint Statistic	**Placebo N = 158**	**LJPC-501 N = 163**	**Total N = 321**
Screening	(N = 158)	(N = 158)	(N = 316)
Mean (SD)	12.72 (3.310)	11.77 (2.839)	12.24 (3.115)
Median (Range)	13.00 (5 – 21)	12.00 (5 – 18)	12.00 (5 – 21)
Day 2, Hour 48	(N = 158)	(N = 163)	(N = 321)
Mean (SD)	13.76 (6.700)	12.69 (6.033)	13.22 (6.382)
Median (range)	13.50 (1 - 24)	11.00 (2 - 24)	12.00 (1 - 24)
Change from Screening	(N = 158)	(N = 158)	(N = 316)
Mean (SD)	1.04 (5.336)	1.05 (5.500)	1.05 (5.410)
Median (Range)	0.00 (−9 –16)	0.00 (−10 – 15)	0.00 (−10 – 16)
p value (van Elteren Wilcoxon)	0.9755		
p value (general linear model)	0.4901		

(Source: The sponsor's Table 35, confirmed by the reviewer's analysis)

3.2.7 Reviewer's Results:

This reviewer was able to confirm the sponsor's primary and secondary endpoints analyses and concurred with the results. There seems no statistical issue that may have impact on the interpretation of the study results.

3.2.8 Conclusions

The study seems to support the superiority of LJPC-501 in increasing MAP.

3.3 Evaluation of Safety

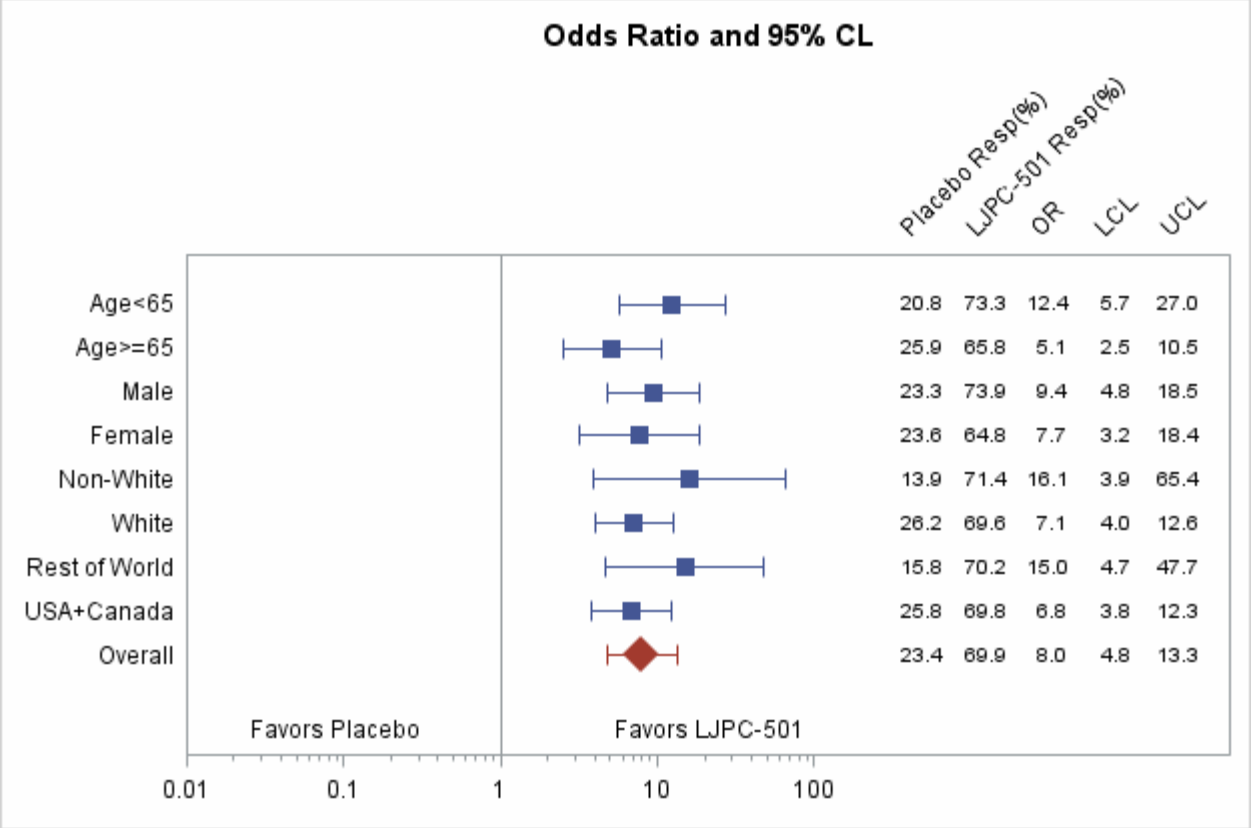
Please refer to Dr. McDowell's review for safety assessment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The primary efficacy analysis was conducted in the subgroups of age, gender, race and geographic region. A consistent result trending in favor of LJPC-501 was demonstrated across all the subgroups (Figure 2).

Figure 2 Subgroup Analyses

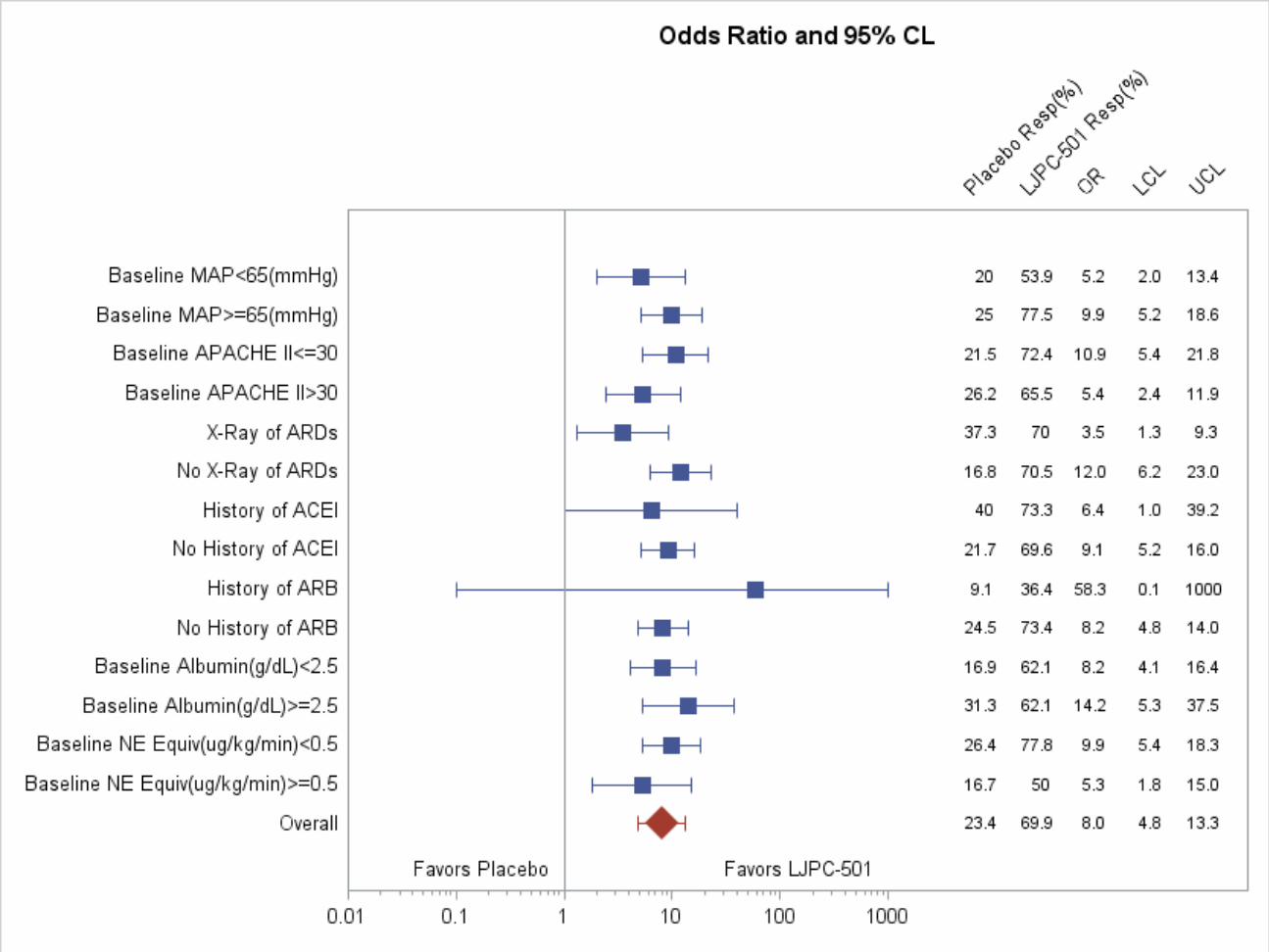


(Source: The reviewer's analysis)

4.2 Other Special/Subgroup Populations

Exploratory subgroup analyses were also conducted in selected special subgroup populations with underlining disease characteristic. The results are in favor of LJPC-501 for most of the subgroups (Figure 3).

Figure 3 Other Subgroup Analyses



(Source: The reviewer's analysis)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Overall the efficacy of LJPC-501 in increasing MAP seems evident. The primary efficacy endpoint of percent responders achieving the target MAP at hour 3 was statistically significantly higher in the LJPC-501 group compared to the placebo group (69.9% and 23.4%, for LJPC-501 and placebo, respectively; $p<0.0001$). The efficacy was also consistent trending in favor of LJPC-501across the subgroups of age, gender, geographic regions and selected special populations with underlining disease characteristics.

5.2 Conclusions and Recommendations

The study seems to support that LJPC-501 is superior in the treatment of catecholamine-resistant hypotension (CRH) compared to the placebo in adults with distributive or vasodilatory shock who remain hypotensive despite fluid and vasopressor therapy.

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QUQUAN LIU
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HSIEN MING J HUNG
11/22/2017