	La Jolla Pharmaceutical Call For Grant Application
Date Issued	April 20, 2017
Deadline for Application	August 15, 2017
Therapeutic Area	Distributive Shock
Purpose of CGA	To increase health care professional (HCP) knowledge and skills related to: • Updated treatment protocols/patterns of distributive shock management • Understand the three blood pressure counter-regulatory systems (adrenal/sympathetic, arginine/vasopressin, renin-angiotensin-aldosterone) • Recognizing patients with clinical refractory hypotension which are a population of distributive shock patients who remain hypotensive despite adequate fluid resuscitation and catecholamine therapy • Novel research and treatment targets for shock management Application of evolving science, new and emerging therapies to optimize the treatment of distributive shock patients
Summary of Health Care Gap	Shock is well characterized, and occurs in 1/3 of ICU patients. Over 50% of patients with shock in the ICU. For shock, mortality is measured in hours[1]. These statistics suggest that it is important to re-examine current management of shock to lower mortality rate and improve patient outcomes. Walsh investigated the relationship between MAP and clinical outcomes in 27,381 patients who had 33,330 non-cardiac surgeries. In these patients, 2,478 (7.4%) experienced acute kidney injury (AKI) and 770 (2.3) experienced myocardial injury. The data also demonstrated that even short durations of a MAP less than 55 mmHg were associated with acute kidney injury and myocardial injury.[2] In a retrospective cohort analysis, Salmasi showed that an intraoperative mean arterial pressure (MAP) below absolute thresholds of 65 mmHg or relative thresholds of 20% were progressively related to both myocardial and

	kidney injury. At any given threshold, prolonged exposure was associated with increased odds.[3] There are multiple treatment algorithms associated with shock. Although minor differences exist, the core management is the same with adequate fluid resuscitation followed by addition of vasopressor therapy.[4] Severe hypotension is associated with significant mortality and the use of high dose catecholamines in these patients is associated with poor outcomes. In a review of literature, Bassi and colleagues summarized results of 13 studies in which inpatient mortality was 47% to 94% when the norepinephrine (NE) dose exceeded 0.1 µg/kg/min[5]. In an observational study that followed 808 patients over a 4-year period who had a principal or secondary diagnosis of septic shock conducted by Brand, the overall in-hospital mortality was 41% (331/808) (95% confidence interval, 38.5% to 44.5%). The patients requiring higher dose and multiple vasopressors, the mortality rate was as high as 92.3% (12/13; 95% CI, 79.4%-100.0%) leading to the conclusion that when a standard full dose of a vasopressor fails to normalize blood pressure in a patient with septic shock, escalation begins to yield diminishing returns as the dose and multiplicity of agents approach practical upper limits.[6] In a prospective observational study of 112 SICU patients 48.2% experienced adverse cardiac events during catecholamine vasopressor therapy. Number of agents infused and the duration of therapy were independently associated with adverse cardiac events. New-onset tachyarrhythmia (49.1%), prolonged elevated heart rate (23.7%), and myocardial cell damage (17.5%) occurred most frequently. Those who developed adverse cardiac events had greater morbidity and mortality.[7] In a regression analysis performed by Sviri, controlling for MAP, creatinine, platelets, ventilation status, APACHE II score, cirrhosis or chronic liver failure, and hematolological malignancy; he demonstrated that high-dose catecholamines were an independent predictor of mortality in patients in the ICU. The increased odds ratio of ICU mortality was 5.1 in patients treated with high-dose catecholamines relative to those treated with low-dose catecholamines.[8]

	In human physiology, blood pressure is under tight counter-regulatory control. The three main systems the body leverages are the sympathetic nervous system, arginine-vasopressin system, and the renin-angiotensin-aldosterone system (RAAS). Despite this, currently only two out of the three systems are being leveraged for the management of hypotension.[9-10] The renin-angiotensin-aldosterone-system (RAAS) is a well described physiologic mechanism that controls blood pressure. The ability of angiotensin II to raise blood pressure in response to either volume depletion or drop in MAP through the AT-1 receptor is well described.[11] Given the high unmet medical need, there still exist a need for better understanding and improvement of patient care in this patient population. There is also a need to better understand novel therapeutic targets to improve management and outcomes for patients.
Potential Learner	Critical care team, intensivists, NP/Pas in critical care, critical care nurses, hospital pharmacists, PNT decision makers
Educational Format	Educational initiative including delivery formats and learning techniques based on adult learning principles and tailored to independently identified gaps of the learners. Grant request should demonstrate the ability to target the educational intervention to health care professional learners with the most need of improving care of critically ill patients. It should show the ability to tailor educational interventions based on gaps in practice associated with clinician, patient and or health system related factors.
Outcomes Measure	At minimum, the evaluation plan must be designed to objectively measure improvements in HCP knowledge and competence (Level 4).
Funding Guidelines	Budget should demonstrate fiscal responsibility and cost effectiveness. Total budget should not exceed $500K. Multi-support is preferred. However, sole support will be considered.
Submission Requirements	When responding to this CGA, please follow the established guidelines for the La Jolla medical education grant submission process. All applications must be

	submitted online at lajollapharmaceuticalgrants.com. Grant applications submitted after the deadline will not be reviewed. The education must be accredited by the appropriate accrediting bodies, be fully compliant with ACCME criteria and the Standards for Commercial Support and must be in accordance with the U.S. Food and Drug Administration's Guidance on Industry Supported Scientific and Educational Activities. If accepted, must attest to the terms, conditions and purposes of an educational grant as described in the La Jolla letter of agreement. Immediately upon reconciliation, Takeda will solely determine if Provider or any Educational Partner made any value transfers in connection with the educational activity that must be reported in connection with Commercial Interest's Transparency Reporting program. Should La Jolla determine that a particular value exchange must be reported, Provider and/or Educational Partner shall provide any information requested by Takeda within thirty (30) days of the request. Provider and Educational Partners shall not withhold any information reasonably required by Commercial Interest in connection with its reporting obligations.
References	1. Sviri S, Hashoul J, Stav I, van Heerden PV. J Crit Care. 2014;29(1):157-160 2. Walsh M, Devereaux PJ, Garg AX, et al. Anesthesiology. 2013;119(3):507-515 3. Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI, Kurz A, et al. Anesthesiology. 2017 Jan;126(1):47-65. 4. Vincent JL, De Backer D. N Engl J Med. 2013;369(18):1726-1734 5. Bassi E, Park M, Azevedo LCP. Crit Care Res Pract. 2013;2013:1-10 6. Brand D, Patrick P, Berger J, Ibrahim, M, Matela A, Upadhyay S, Spiegler P. J Pain Symptom Manage. 2017 Jan 3 7. Houwink API, Rijkenberg S, Bosman RJ, van der Voort PHJ. Crit Care. 2016;20:56. 8. Sviri S, Hashoul J, Stav I, van Heerden PV. J Crit Care. 2014;29(1):157-160 9. Trotter J. AANA J. 2012;80(1):55-60. 10. Moranville MP, Mieure KD, Santayana EM. J Pharm Pract. 2011;24(1):44-60 11. Corrêa TD, Takala J, Jakob SM. Crit Care. 2015;19:98
