La Jolla Pharmaceutical Company (LJPC)

Initiation Report

La Jolla Pharmaceutical Company (NasdaqCM: LJPC) is focused on the development of innovative therapies for life-threatening conditions. La Jolla is currently evaluating their lead candidate LJPC-501 in a registration-directed Phase 3 trial for distributive shock patients with clinically-refractory or catecholamine-resistant hypotension (CRH), and expects to report topline results in the first quarter. Existing third-line regimens expose CRH patients to heightened risk of toxicities and mortality, and a substantial proportion remain refractory to treatment. La Jolla is also developing LJPC-401 for inherited and acquired iron overload disorders, and has reached an agreement with the EMA on the design of a pivotal Phase 2 study to evaluate LJPC-401 in beta thalassemia. The trial is expected to launch in mid-2017.

Key Points of Discussion

- **Lead Program LJPC-501 is a Novel Vasopressor for Clinically-Refractory Hypotension (CRH).** La Jolla’s lead candidate LJPC-501 is a proprietary, synthetic formulation of the human peptide angiotensin II, that is being developed as a novel vasopressor treatment for distributive shock, whereby insufficient blood flow to maintain proper organ perfusion leads to organ damage and death. These patients are first treated with fluid resuscitation and then catecholamines like norepinephrine. However, as many as 40% of patients do not achieve an adequate mean arterial blood pressure (MAP) with well-tolerated doses of catecholamines. For these patients, either increasing the initial catecholamine dose or adding on a second vasopressor (catecholamine or vasopressin) exposes the patient to toxicity and a heightened mortality risk exceeding 80%. These patients are considered to have clinically-refractory or catecholamine-resistant hypotension (CRH).

- **Opportunity for LJPC-501 in CRH Worth Nearly $500 Million.** LJPC-501 is a complementary treatment for CRH patients that raises MAP through an alternate biological pathway relative to catecholamines and vasopressin. Thus, for some patients refractory to existing treatments, LJPC-501 may offer a third vasopressor pathway to activate in order to increase MAP. In addition, depending on the safety and efficacy data generated in the ongoing ATHOS 3 Phase 3 trial, LJPC-501 may provide comparable efficacy in raising MAP to existing third-line options with a better tolerability profile. Our base scenario assumes that the Company hits the MAP primary endpoint and could capture nearly $500 million in peak sales. The data from the trial will play an important role in shaping where LJPC-501 fits into the current treatment paradigm for distributive shock. There is upside potential if the trial shows a benefit on mortality or hospital length of stay. If approved, LJPC-501 may be well-positioned to address the pressing need for novel vasopressors.

Expected Upcoming Milestones

- Q1 2017 – Topline data from registration-directed Phase 3 for LJPC-501 in CRH.
Readout from ATHOS 3 Phase 3 Trial Provides Near Term Catalyst. La Jolla expects to report topline results from the registration-directed ATHOS 3 Phase 3 trial in the first quarter of this year. The study is a randomized, placebo-controlled trial evaluating the safety and efficacy of LJPC-501 in the treatment of CRH patients. La Jolla has reached an agreement on a Special Protocol Assessment (SPA) with the FDA on the trial design and the primary efficacy endpoint, increased mean arterial pressure (MAP). Given that the role of angiotensin II in raising blood pressure is very well-characterized, the Company has a good chance of meeting this endpoint. The trial enrolled CRH patients receiving high dose catecholamines with or without vasopressin, so the results will provide details on the potential of LJPC-501 as a last-line option as well as ahead of vasopressin. The study is also over-enrolled with 345 patients, up from its original 315 target.

Reductions in Mortality and Length of Stay Could Increase Use Ahead of Existing Third-Line Agents. The Phase 3 trial for LJPC-501 includes exploratory endpoints on the impact of LJPC-501 on mortality and hospital length of stay (LOS). Positive effects on either of these endpoints would likely drive broader formulary access and greater physician use, particularly ahead of third-line agents following failure of an initial catecholamine dose. In particular, a reduction in the LOS would have a meaningful impact on healthcare expenditure for these patients and would provide a pharmacoeconomic rationale for greater reliance on LJPC-501 instead of other agents once an initial catecholamine dose is determined to be inadequate. Due to the larger patient numbers, there is the potential for expanded use if either of these endpoints is met.

Pilot Study Provided Proof-of-Concept for Use of Angiotensin II to Treat CRH. Investigators at George Washington University conducted a randomized pilot study with 20 patients who received dose-titrated angiotensin II on top of therapy with catecholamines ± vasopressin. The trial demonstrated that distributive shock patients receiving angiotensin II could maintain an adequate MAP with lower doses of catecholamines. Overall, 80% of the patients in the trial had a response to the drug. In addition, there were no major differences in safety between arms of the study. Following these positive results, La Jolla licensed the intellectual property from the university and improved upon the formulation prior to moving into Phase 3.

Pricing Will Play Key Role in Shaping Formulary Access for New Agents. We expect La Jolla to price LJPC-501, if approved, at a premium to vasopressin. How large a premium will be dictated by the overall quality of the Phase 3 safety and efficacy data and whether or not a benefit is seen on the mortality rate or length of hospital stays in the trial. Pricing will also be an important determinant of formulary access and restrictions by line of therapy. The trial is designed to test use of LJPC-501 as an adjunctive therapy in the last-line setting (in combination with high dose catecholamines and vasopressin) as well as ahead of vasopressin (in combination with high dose catecholamines). If the drug is approved, pricing will likely play an important role in shaping how broadly LJPC-501 is used in the third-line setting ahead of vasopressin or high dose catecholamines and whether any formulary restrictions are placed on the drug.

LJPC-401 for Iron Overload Disorders Like Hereditary Hemochromatosis, Beta Thalassemia, and Sick Cell Disease. La Jolla is developing a synthetic form of human hepcidin, known as LJPC-401, for the treatment of iron overload. This condition is caused by genetic disorders or frequent blood transfusions, and results in the accumulation of iron in the heart, liver, and other vital organs. Excess iron is deposited in the organs and long-term exposure can lead to tissue damage, organ failure, and death. The Centers for Disease Control and Prevention (CDC) estimate that over one million patients in the US experience iron overload each year.¹ Current treatment protocols focus on iron

¹ http://www.cdc.gov/ncbddd/hemochromatosis/index.html
reduction strategies using phlebotomy or iron chelators, but many patients are intolerant or fail to improve with these therapies.

- **Initial Focus for LJPC-401 on Beta Thalassemia Indication in Europe.** La Jolla has completed a Phase 1 study, which demonstrated that LJPC-401 was well-tolerated and effective at lowering serum iron levels. The Company has reached an agreement with the EMA on the design of a pivotal study for LJPC-401 in patients with beta thalassemia and expects to initiate this study in the middle of 2017. The Company has received Orphan Drug designation from the EMA for LJPC-401 in the beta thalassemia indication and has also received a positive recommendation for Orphan designation for sickle cell disease (SCD). Demonstration of safety and efficacy in the beta thalassemia patient population would allow for La Jolla to pursue additional iron overload indications such as sickle cell disease (SCD) and myelodysplastic syndrome (MDS).

**Financial Discussion**

**Third Quarter 2016 Financial Results.** On November 3, 2016, La Jolla announced financial results for the third quarter of 2016. The Company reported an operating expenses of $21.3 million for the third quarter, compared with $11.1 million in the third quarter of 2015. This increase in operating costs was primarily due to increased research and development expenses. La Jolla reported a net loss of $21.3 million, or $1.23 per share, for the third quarter, compared with a net $10.5 million, or $0.70 per share, loss in the same period in 2015. As of September 30, 2016, the Company had cash and cash equivalents of $85.0 million, which they consider sufficient to fund operations into 2018.
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Company Description

La Jolla Pharmaceutical Company is a biopharmaceutical company focusing on the development and commercialization of therapeutics for a range of life-threatening conditions. The development pipeline is shown in Figure 1. The Company’s lead candidate is LJPC-501, a proprietary formulation of the human peptide angiotensin II, that is being developed as a novel vasopressor treatment for distributive shock, whereby insufficient blood flow to maintain proper organ perfusion leads to organ damage and death. These patients are first treated with fluid resuscitation and then catecholamines like norepinephrine. However, as many as 40% of patients do not achieve an adequate mean arterial blood pressure (MAP) with well-tolerated doses of catecholamines. For these patients, either increasing the initial catecholamine dose or adding on a second vasopressor (catecholamine or vasopressin) exposes the patient to toxicity risks and a heightened mortality risk exceeding 80%. These patients are considered to have clinically-refractory or catecholamine-resistant hypotension (CRH).

La Jolla hopes to demonstrate that LJPC-501 add-on therapy can allow the achievement of adequate MAP in a refractory shock population and the reduction in catecholamine dosing within the tolerable range. Proof-of-concept for angiotensin II add-on therapy was demonstrated by investigators at George Washington University in a 20 patient pilot study. La Jolla then in-licensed the intellectual property and is currently conducting a Phase 3 trial evaluating a proprietary angiotensin II formulation LJPC-501. The Company expects to report data later this quarter. If approved, La Jolla could launch LJPC-501 with a targeted sales force initially focusing on high-volume medical centers.

Figure 1. La Jolla’s Developmental Pipeline

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<tr>
<td><strong>LJPC-501 – Angiotensin II</strong></td>
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<td>Catecholamine-Resistant Hypotension</td>
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<td><strong>LJPC-401 – Human Hepcidin</strong></td>
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<td>Beta Thalassemia</td>
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<td>LJPC-30Sa/b</td>
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<tr>
<td>Rare Genetic Disorders</td>
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Source: LifeSci Capital

La Jolla is also developing LJPC-401, a synthetic form of human hepcidin, for the treatment of iron overload. This condition is either inherited through certain genetic disorders or acquired through frequent blood transfusions, and results in the accumulation of iron in the heart, liver, and other vital organs. Long-term exposure to excess iron can damage vital organs and lead to organ failure. La Jolla has conducted a Phase 1 study evaluating LJPC-401 in patients with iron overload, which demonstrated that the drug was well-tolerated and effective at lowering serum iron levels.
in a dose-dependent manner. La Jolla has reached an agreement with the European Medicines Agency (EMA) on the design of a pivotal trial for patients with beta thalassemia, an orphan indication that results in iron overload. The Company expects to launch this trial in the middle of 2017.

In May 2015, La Jolla entered into an exclusive option agreement to acquire the Indiana University Research and Technology Center’s (IURTC) intellectual property rights covering next-generation gentamicin derivatives LJPC-30Sa and LJPC-30Sb, and plans to develop these compounds for bacterial infections. The Company has a second agreement with IURTC and the University of Alabama, Birmingham to develop LJPC-30Sa and LJPC-30Sb for rare genetic disorders including cystic fibrosis and Duchenne muscular dystrophy (DMD). La Jolla recently met with the FDA and received positive feedback on a proposed design for a Phase 1 trial.

Clinically-Refractory Hypotension (CRH)

Shock is a form of circulatory failure, whereby there is insufficient perfusion of blood to vital organs of the body. This can result very rapidly in organ damage and death. Shock is fairly common, affecting roughly 1 in 3 patients in the intensive care unit (ICU). There are several types of shock, including:

- **Distributive Shock** – Shock resulting from the excessive vasodilation and inappropriate distribution of blood in the vasculature. Septic shock is the most common form of distributive shock.
- **Cardiogenic Shock** – Pump failure whereby the heart cannot keep up with the demands of the body.
- **Hypovolemic Shock** – Shock resulting from the loss of 20% or more of the body’s blood supply.
- **Obstructive Shock** – Inadequate circulation resulting from an obstruction to blood circulation.

Distributive shock makes up roughly 65% of all cases of shock, as shown in Figure 2. Distributive shock can result from sepsis, anaphylaxis, brain injury, hepatic insufficiency, systemic inflammatory response syndrome (SIRS), adrenal insufficiency, cardiac dysfunction, cardiac failure, and a range of other conditions. Normal blood pressure is in the range of 75 – 110 mmHg, and the threshold for severe hypotension is typically a mean arterial pressure (MAP) less than 60-65 mmHg. If not rapidly corrected, this condition can become life-threatening. Diagnosis is typically based on clinical, hemodynamic, and biochemical signs, including the following observations: 1) systemic arterial hypotension is present; 2) signs of tissue hypoperfusion, which may be most readily detected by assessing cutaneous, renal, and neurological function; 3) elevated blood lactate levels indicative of altered cellular metabolism.

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Low MAP (<65 mmHg) and high lactate (>2 mmol/L) levels at admission are independent predictors of ICU mortality.\(^4\) Restoring and maintaining a MAP greater than 65 mmHg is an immediate goal of treatment and is associated with lower mortality. Figure 3 highlights the probability of survival as a function of ICU length of stay, showing a breakdown of data by MAP and lactate levels. Patients with a MAP less than 65 mmHg and a lactate level over 2 mmol/L have the highest mortality rates, while a MAP over 65 mmHg and lactate levels below 2 mmol/L were associated with lower mortality rates.

\[\text{Source: Walsh et al., 2013}\]

\[\text{Figure 3. Survival Curves as a Function of ICU Length of Stay, MAP, and Lactate Levels}\]

\[\text{Source: Walsh et al., 2013}\]

\[\text{Aletta, P, et al., 2016. The association between lactate, mean arterial pressure, central venous oxygen saturation and peripheral temperature and mortality in severe sepsis: a retrospective cohort analysis. Critical Care, 20, pp56.}\]
Most patients with severe hypotension end up in the intensive care unit (ICU), originating from the operating room, emergency department, or other hospital departments. Treatment for hypotension is usually independent of the cause and involves the use of agents that can rapidly raise blood pressure. Despite treatment, more than 50% of patients die in the hospital, and nearly 40% of the deaths result from progressive refractory hypotension. This highlights the need for novel vasopressor agents that can complement the existing treatment landscape.

**Treatment.** The first-line therapy for severe hypotension is fluid resuscitation. Roughly 92% of patients are then administered an intravenous catecholamine, such as norepinephrine, dopamine, or epinephrine, which is the second-line treatment option. These agents are signaling molecules and neurotransmitters that are important modulators of blood pressure. Norepinephrine is typically the preferred vasopressor in treating shock patients. Epinephrine, while a stronger vasopressor than norepinephrine, can cause cardiac arrhythmias, and dopamine has adverse effects on the hypothalamic–pituitary axis that induce immunosuppression.6

**Figure 4** highlights the typical treatment paradigm for patients with severe hypotension that do not respond to fluids. While many severe hypotension patients are successfully treated with catecholamines, approximately 40% of patients do not achieve an adequate MAP. These patients are considered to be resistant to catecholamines—referred to as clinically-refractory hypotension (CRH) or catecholamine-resistant hypotension. At this point, the physician must consider placing the patient on a high dose of catecholamines (>0.2 µg/kg/min) or adding a second vasopressor (catecholamine or vasopressin) despite the elevated risks of toxicities and mortality associated with these regimens.7,8 A meta-analysis of 28 randomized studies evaluating 6 vasopressors alone or in combination found that none of the regimens showed superiority in terms of impacting mortality rates.9

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Physicians managing a patient that fails an initial catecholamine dose are faced with a life-threatening situation and limited treatment options. Some of the problems at this point in treatment are:

- **Heightened Mortality** – Patients with severe distributive shock treated with low doses of catecholamines have a 50% mortality rate. However, this jumps to over 80% when high dose catecholamines are used.\(^{10,11}\) The higher the dose of catecholamines goes above 0.2 µg/kg/min, the greater the mortality risk.


- **Limited Efficacy of Vasopressin** – Vasopressin is also used as an adjunct therapy to low dose norepinephrine to raise MAP in CRH patients. The drug is typically added after failing high dose catecholamines, but may also be used instead of escalating the catecholamine dose. The VAASS clinical trial showed that there was no significant difference between vasopressin add-on and high dose catecholamine regimens in terms of mortality (left) and MAP (right). This result is shown in **Figure 5**. Vasopressin use can result in catecholamine dose sparing and lower toxicity, but the drug has not been shown to improve outcomes. Roughly 50% of patients treated with vasopressin do not reach an adequate MAP, forcing the use of rescue therapies like methylene blue or steroids, which have not been substantiated with clinical evidence.

**Figure 5. Comparison of Norepinephrine and Vasopressin on MAP and Mortality**

- **Toxicities** – At high doses, catecholamines are associated with a range of toxicities including damage to the heart. **Figure 6** shows the incidence of cardiac-related adverse events as a function of catecholamine dose and duration of therapy in a prospective observational study in 112 patients in the surgical intensive care unit (SICU). Greater numbers of vasopressors infused (left) and longer durations of therapy (right) were associated with higher rates of cardiac events. Overall, 48% of the SICU patients experienced a cardiac adverse event during catecholamine therapy; the most common AEs were new-onset tachyarrhythmia (49%), prolonged

elevated heart rate (24%), and myocardial injury (18%). Vasopressin can also induce damage through extreme vasoconstriction that can induce digital, mesenteric, or coronary ischemia.\textsuperscript{16,17,18}

**Figure 6. Incidence of Cardiac-Related Adverse Events vs. Catecholamine Dose and Duration of Therapy**

![Graph showing incidence of cardiac-related adverse events vs. catecholamine dose and duration of therapy.]

*Source: Schmittinger et al., 2012*

**Low MAP Associated with Serious Adverse Events** – CRH patients are at greater risk of kidney and cardiac injury.\textsuperscript{19} **Figure 7** shows the probably of acute kidney (A) or cardiac (B) injury as a function of lowest MAP, highlighting the high rates of injury that can occur in CRH patients. Even short durations of time with a MAP below 55 mmHg was sufficient to substantial increase the odds ratios for acute kidney and cardiac injury.

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The high rate of mortality for CRH patients underscores the need for additional vasopressor agents that can help patients achieve an adequate MAP. La Jolla’s LJPC-501 is a complementary treatment for CRH patients that raises blood pressure through an alternate biological pathway relative to catecholamines and vasopressin. Thus, for some patients refractory to existing treatments, LJPC-501 may offer a third vasopressor pathway to activate in order to increase MAP. In addition, depending on the safety and efficacy data generated in the ATHOS 3 Phase 3 trial, LJPC-501 may provide comparable efficacy in raising MAP to existing third-line options with a better tolerability profile and lower risk of mortality. The data from the trial will play an important role in shaping where LJPC-501 would be used in the current treatment paradigm for distributive shock.

**LJPC-501: Synthetic Angiotensin II for Clinically-Refractory Hypotension**

La Jolla’s drug candidate LJPC-501 is a proprietary, synthetic formulation of the human peptide angiotensin II, which is an important component of the renin-angiotensin aldosterone system (RAAS) that regulates blood pressure. **Figure 8** illustrates the 3 pathways in the body that regulate blood pressure and points out that there are no existing treatments for distributive shock that target the RAAS. Catecholamines boost blood pressure through actions on the sympathetic nervous system, while vasopressin activates the arginine-vasopressin system. The RAAS is targeted by many hypertension drugs, making it a well-validated target for modulating blood pressure. By activating the RAAS, LJPC-501 provides a novel option for elevating MAP in patients with refractory hypotension.
**Mechanism of Action.** LJPC-501 is designed to increase blood pressure by acting as a synthetic mimic of angiotensin II, a signaling molecule naturally found in the human body. Angiotensin II binds to angiotensin II type 1 (AT$_1$) receptors, which are a type of G-protein coupled receptors (GPCR) located on vascular smooth muscle cells. Activation of this receptor leads to contraction of vascular muscle, thereby increasing blood pressure. It also acts in the kidneys to increase sodium reabsorption and has endocrine effects that further promote increased blood pressure.

As an endogenous molecule, angiotensin II is part of the renin-angiotensin aldosterone system (RAAS) and is produced in response to blood volume depletion and/or decreased MAP. The production starts with renin secretion from the kidney to stimulate cleavage of angiotensinogen into angiotensin I. ACE then cleaves angiotensin I into angiotensin II, and the peptide increases blood pressure via several mechanisms mediated mainly by the AT$_1$ receptors. The effects of angiotensin II include:

- Vasoconstriction.
- Aldosterone secretion.
- Sodium and water reabsorption.
- Vasopressin release.
- Release of Pro-inflammatory cytokines.

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Preclinical Data.

**Sepsis-Induced Hypotensive Ewe Model.** Investigators tested the potential of angiotensin II as a vasopressor treatment for severe hypotension, using an animal model of sepsis.\(^\text{21}\) In this experiment, conscious sheep received intravenous infusions of live *E. coli* to induce sepsis and were then randomized to treatment with either angiotensin II or vehicle. **Figure 9** highlights the effect of angiotensin II (Ang II) or vehicle on mean arterial pressure (MAP), showing that angiotensin II was associated with a significant increase in MAP relative to vehicle during the treatment period (III). Period I is a control period, and period II is a sepsis control period prior to the administration of treatment. In this trial, angiotensin II led to reduced renal blood flow, although there were no other adverse effects on blood flow to other organs.

**Figure 9. Effects of Angiotensin II in Sepsis-Induced Hypotensive Model**

![Figure 9](image)

*Source: Wan et al., 2009*

**Septic Shock Porcine Model.** Investigators generated a porcine model of septic shock through 12 hours of fecal peritonitis.\(^\text{22}\) As shown in **Figure 10**, 16 pigs were randomized to receive fluid resuscitation and norepinephrine (gray circles; \(n = 8\)) or angiotensin II (orange squares; \(n = 8\)). In this experiment, angiotensin II reversed sepsis-induced hypotension to a similar degree as norepinephrine. The investigators also evaluated a separate group (black triangles; \(n = 8\)) that was pre-treated for a week with enalapril, an angiotensin-converting enzyme (ACE) inhibitor, prior to receiving fluid resuscitation and norepinephrine. The pigs pretreated with enalapril, which inhibits the production of angiotensin II, did not reach the target MAP, suggesting that there may be a synergistic effect between norepinephrine and angiotensin II. This study confirmed the potential of angiotensin II to treat severe hypotension in another animal.


model and provided a rationale for exploring its utility as a treatment for patients with distributive shock in clinical trials.

**Figure 10. Angiotensin II Has Similar Effect on MAP to Norepinephrine in Porcine Model**

![Graph showing comparison of MAP effects](image.png)

BL: baseline; EOP: end of observation period; RP: resuscitation period.

*Source: Correa et al., 2014*

**Safety Profile.** Angiotensin II is a naturally-occurring signaling molecule in the human body, so it is expected to have a favorable safety and tolerability profile. In a pilot study evaluating angiotensin II in 20 CRH patients, the drug appeared to be well-tolerated. The most common adverse event attributed to angiotensin II was hypertension, which is expected given its mechanism of action. There are no expected overlapping toxicities with catecholamines or vasopressin. The ongoing Phase 3 study is testing LJPC-501 as an add-on therapy for patients receiving high dose catecholamines with or without vasopressin, so the trial will generate important safety information on the addition of LJPC-501 to these regimens.

**Expected Commercial Strategy for LJPC-501**

Since LJPC-501 is intended for use exclusively in the intensive care unit (ICU), gaining formulary access will be a critical step in its commercialization, if it is approved. Once on formulary, the Company could promote use of LJPC-501 in the broadest possible subset of hypotensive patients with additional data to fully characterize the clinical value of the drug. We expect that an initial launch would consist of a small, targeted sales force focused on high-volume medical centers and then begin to scale up from there. Within the hospital system, a sales team would need to target critical care physicians, ICU nursing teams, and pharmacy directors. Some of the key facets expected for La Jolla’s commercialization effort include:

- **Gaining Formulary Access** – La Jolla expects that physician championing will be important for triggering formulary reviews of LJPC-501. Efficacy in raising mean arterial pressure (MAP) is likely the primary criterion for formulary inclusion.
Surviving Sepsis Campaign (SSC) Guidelines – The SSC guidelines are a definitive set of guidelines for treating shock patients. Most intensivists follow the SSC guidelines to some degree, so the inclusion of LJPC-501 in these guidelines could have a very significant effect on formulary access and adoption. Because the pivotal trial allowed for LJPC-501 to be added to high-dose catecholamines with or without vasopressin, inclusion in the SSC guidelines would likely involve description of both second-line and third-line use.

Outcomes Data – The Phase 3 trial for LJPC-501 includes secondary endpoints on the impact of LJPC-501 on mortality and hospital length of stay (LOS). Positive effects on either of these endpoints would likely drive broader formulary access and greater physician use, particularly ahead of other third-line agents like vasopressin or even high dose catecholamines. However, it is worth noting that there is a pressing need for new pressor medications independent of whether or not a mortality or LOS benefit is observed.

Pricing – We expect La Jolla to price LJPC-501, if approved, at a premium to vasopressin. How large a premium will be dictated by the overall quality of the Phase 3 safety and efficacy data and whether or not a benefit is seen on the mortality rate or length of hospital stays in the trial. Pricing will also be an important determinant of formulary access and restrictions by line of therapy. However, the life-threatening nature of CRH likely gives physicians a fair amount of discretion.

Real-World Evidence – Generating real-world evidence on the benefit of LJPC-501 will be critical to driving adoption among the broadest possible range of medical centers.

Market Information

Epidemiology. Figure 11 estimates the population of patients experiencing distributive shock and those who do not adequately respond to catecholamine therapy. There are roughly 432,000 patients who experience distributive shock each year in the US and 92% of these patients are treated with catecholamines. Among these patients, about 159,000 or 40% do not reach an adequate MAP following an initial dose of catecholamines, representing the total population of CRH patients in the US. We define resistance to catecholamines as a dose exceeding 0.2 µg/kg/min.

Figure 11. US Population of CRH Patients

| Number of patients with distributive shock | 432,000 |
| Number of patients treated by catecholamines (92%) | 397,000 |
| Inadequate MAP after initial catecholamine (40%) | 159,000 |

Source: LifeSci Capital

Market Size. There are currently very few options available for patients who do not respond to fluid resuscitation or an initial dose of catecholamines. The treatment strategy for these CRH patients is shown in Figure 12. Once a patient fail to reach an adequate MAP with an initial dose of catecholamines, the next step is usually to add a second
vasopressor, either by increasing the initial catecholamine dose or adding on a second catecholamine. A physician may also use vasopressin ahead high dose catecholamines as a third-line agent. Elevating catecholamines expose the patient to the toxicity risks as well as a heightened mortality risk exceeding 80%. We estimate that roughly 40% of patients don’t achieve an adequate MAP with this strategy, leaving roughly 95,000 to then receive vasopressin add-on therapy. In addition to the toxicity risks associated with vasopressin use, only about 50% of these patients achieve an adequate MAP with vasopressin, leaving 48,000 with only rescue therapies.

**Figure 12. Opportunity for LJPC-501 as a Second-Line and Third-Line Treatment for CRH Patients**

<table>
<thead>
<tr>
<th>Initial Catecholamine Dose (≤ 0.2µg/kg/min)</th>
<th>Adequate MAP</th>
<th>Inadequate MAP</th>
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</thead>
<tbody>
<tr>
<td>Adequate MAP</td>
<td>55%</td>
<td>40%</td>
</tr>
</tbody>
</table>

**Increase Initial Catecholamine Dose OR Add 2nd Catecholamine (up to 0.4µg/kg/min)**

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<thead>
<tr>
<th>Adequate MAP</th>
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<td>40%</td>
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**Market Opportunity:**
- 159,000

**Add Vasopressin**

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<tr>
<th>Adequate MAP</th>
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<td>50%</td>
<td>50%</td>
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</tbody>
</table>

**Market Opportunity:**
- 95,000

**Rescue Therapy**
(Methylene Blue, Rescue Steroids, etc.)

**Market Opportunity:**
- 48,000

Source: LifeSci Capital

There is an obvious opportunity for La Jolla’s LJPC-501 as a last-line option, since these patients have exhausted all existing treatments. In addition, La Jolla’s Phase 3 trial is testing LJPC-501 as a treatment ahead of vasopressin, and depending on the results of the trial, it could be used earlier, ahead of vasopressin or potentially even high dose catecholamines. In **Figure 13**, we conducted a scenario analysis for the potential market opportunity for use of LJPC-501 at three points in the treatment paradigm: last-line, ahead of vasopressin, and ahead of all third-line options. It is
worth noting that increased use ahead of all third-line agents would decrease the number of patients treated in the last-line setting. We base our estimate on the following assumptions:

- **Market Penetrations** – We assume a high penetration rate for last-line use, since there are no alternative treatment options. We use a range of 50% to 90% for last-line therapy. Use ahead of vasopressin will be shaped by the safety and efficacy data from the Phase 3 trial, as well as pricing and secondary endpoint data. We estimate the range for use ahead of vasopressin to be 10% to 50%. Use ahead of all third-line options is likely to be minimal initially, but a clinically meaningful impact on mortality or length of stay (LOS) in the hospital could encourage the use of LJPC-501 as a third-line option in some patients. We estimate a range of 5% to 15% for use ahead of all third-line options.

- **Pricing** – For our estimate, we use prices of $4,000, $6,000, and $8,000. These prices represent a substantial premium to Endo’s Vasostrict (vasopressin), but are still at the low end of the range of hospital-based drugs reimbursed under DRG reimbursement systems.

**Figure 13. Scenario Analysis of LJPC-501 Market Opportunity**

### Last-Line Therapy for CRH Patients

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### Use Ahead of Vasopressin for CRH Patients

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### Ahead of All Third-Line Options for CRH Patients

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<td>144 M</td>
<td>173 M</td>
<td>202 M</td>
<td>230 M</td>
<td>259 M</td>
</tr>
</tbody>
</table>

Source: LifeSci Capital
At a price of $6,000, capturing 70% of the last-line market, 30% of the market ahead of vasopressin, and 10% of market ahead of high-dose catecholamines in CRH patients would translate into annual sales for La Jolla of nearly $500 million. In 2016, through the month of November, Endo Pharmaceuticals (NasdaqGS: ENDP) reached $329 million in sales for *Vasostrict* (vasopressin), despite a somewhat weak efficacy profile and associated risks of toxicity. Vasopressor sales are shown in Figure 14. This highlights the pressing need that remains in the market for novel options to treat CRH patients. If La Jolla demonstrates that LJPC-501 can raise MAP without the elevated risk of toxicity associated with high-dose catecholamines or vasopressin, then the Company will be well-positioned to capture a meaningful portion of the CRH market.

**Figure 14. Total Market for Pressor Agents to Treat Distributive Shock**

A synthetic formulation of angiotensin II was evaluated in a pilot study in CRH patients at George Washington University. The pilot study demonstrated that angiotensin II could safely raise blood pressure in patients with distributive shock and permitted the use of lower doses of catecholamines than would normally be required to achieve an adequate MAP in CRH patients. Following these positive results, La Jolla in-licensed the intellectual property and is currently evaluating LJPC-501, a proprietary formulation of synthetic angiotensin II, in an ongoing Phase 3 trial. La Jolla has reached an agreement on a Special Protocol Assessment (SPA) with the FDA on the trial design and the primary efficacy endpoint, increased mean arterial pressure (MAP). Given that the role of angiotensin II in raising blood pressure is very well-characterized, the Company has a good chance of meeting this endpoint. The Company expects to complete the trial and report topline data later this quarter.
ATHOS (Angiotensin II for the Treatment of High-Output Shock) Phase 1 Trial

Investigators at George Washington University conducted a randomized pilot study with 20 patients who received dose-titrated angiotensin II on top of therapy with catecholamines ± vasopressin. The trial demonstrated proof-of-concept for the use of angiotensin II as a vasopressor in distributive shock and indicated a catecholamine-sparing effect. Following these positive results, La Jolla licensed the intellectual property from the university and improved upon the formulation prior to moving into the Phase 3 trial.

**Trial Design.** The trial enrolled 20 patients who had distributive shock and a cardiovascular Sequential Organ Failure Assessment (SOFA) score of 4. The SOFA score is a numerical assessment of the function of 6 organs. It is graded from 0 to 4, where 4 equals the greatest loss of function. Patients were randomized 1:1 to receive either angiotensin II or placebo on top of standard of care, which was norepinephrine infusion plus vasopressin, epinephrine, and/or phenylephrine infusions. Angiotensin II infusion was started at 20 ng/kg/minute and dose-titrated hourly for each patient to maintain a mean arterial pressure (MAP) of 65 mmHg. Certain adjustments to norepinephrine were also allowed. The study drug or placebo was administered for a total of 6 hours. The primary endpoint was the change in norepinephrine dose needed to maintain a MAP of 65 mmHg. Secondary endpoints were the effect on urine output, serum lactate, cardiac output, and 30-day mortality.

**Trial Results.** The trial showed that angiotensin II could be used as vasopressor in distributive shock to raise MAP. The investigators found that angiotensin II treatment resulted in a substantial drop in the norepinephrine dose necessary to maintain patient MAP above 65 mmHg. During the first hour, the mean norepinephrine dose was 27.6 ± 29.3 µg/min for the placebo group and 7.4 ± 12.4 µg/minute in the angiotensin II cohort (p=0.06). In total, 80% of patients showed a response to the drug. **Figure 15** shows the mean norepinephrine dose following concurrent treatment with angiotensin II or placebo over 6 hours of treatment. On average, patients on standard of care and placebo received a steady dose of norepinephrine during the study. There was no difference in mortality between the two groups (angiotensin II: 50%; placebo: 60%; p = 1.0), although the trial was not powered to detect a difference on this endpoint. The trial demonstrated strong proof-of-concept with angiotensin II as a potential vasopressor treatment and importantly determined appropriate doses for future clinical development.

---

The most common treatment-emergent adverse event was hypertension, which occurred in 20% of the angiotensin II-treated patients. Metabolic alkalosis was reported in four patients in the treatment arm and no patients in the placebo group. There was no significant difference in 30-day mortality between the two cohorts (p=1.00), although this pilot study was not powered for this endpoint.

ATHOS 3 Phase 3 Trial

Based on the encouraging proof-of-concept results from the pilot trial, La Jolla has initiated a Phase 3 study evaluating LJPC-501 in CRH patients. The trial is assessing the safety and efficacy of LJPC-501 as an add-on vasopressor treatment for ICU patients with distributive shock. The Company has reached an SPA agreement with the FDA, permitting the use of increased MAP as the primary endpoint. Given the well-characterized mechanism through which angiotensin II acts to increase blood pressure, the trial has a good chance of meeting its primary endpoint. Data from the trial are expected later this quarter.

**Trial Design.** The study is a randomized, double-blind, placebo-controlled Phase 3 trial evaluating LJPC-501 in 345 CRH patients. The trial is being conducted under an SPA agreement with the FDA, which includes the use of MAP as the primary efficacy endpoint. The trial enrolled patients who were considered resistant to catecholamines, defined in the trial as patients who require a total catecholamine dose greater than 0.2 µg/kg/min for at least 6 hours to maintain a MAP between 55 and 70 mmHg. These CRH patients, treated already with high dose catecholamines ± vasopressin, are then randomized to receive an add-on of either LJPC-501 or placebo treatment via IV infusion. The primary endpoint of the study is increased MAP, defined as achieving a MAP of 75 mmHg or greater after 3 hours or a 10 mmHg increase from baseline MAP. The key secondary endpoint of the trial is the change in cardiovascular (CV)

24 https://clinicaltrials.gov/show/NCT02338843
and total Sequential Organ Failure Assessment (SOFA) scores at 48 hours. Patients enrolled in the trial continue to receive treatment for up to 7 days. La Jolla and the FDA have reached an agreement that this trial will provide a sufficient safety database for review and consideration of approval. Therefore, if the study is positive, it alone may be sufficient for approval.

The trial also includes a number of exploratory endpoints, including:

- Achievement of a MAP greater than 75 mmHg at hour 1 and hour 2.
- Mortality at 7 days and 28 days.
- Change in heart rate between 0-3 hours and 3-48 hours.
- Change in vasopressor dosing between 3-48 hours.

**Competitive Landscape**

**Lack of Effective Agents for Patients Not Adequately Controlled with Catecholamines.** There is a delicate balance between safety and efficacy in CRH patients, and resistance to catecholamines complicates treatment. Distributive shock is life-threatening, but high doses of catecholamines also lead to cardiac toxicity and heightened mortality risk in CRH patients. Vasopressin, another agent used in conjunction with catecholamines to treat CRH patients, can lower the dose of catecholamines used, but this has not shown a benefit in patient survival. Also, roughly 50% of patients at this stage of treatment still do not reach an adequate MAP. For these patients, there are no clinically-validated treatment options. The high rate of mortality for CRH patients underscores the need for additional vasopressor agents that can help patients achieve an adequate MAP.

La Jolla’s treatment strategy offers a logical solution to this problem. LJPC-501 is a complementary treatment for CRH patients that raises blood pressure through an alternate biological pathway relative to catecholamines and vasopressin. Thus, for some patients refractory to existing treatments, LJPC-501 may offer a third vasopressor pathway to activate in order to increase MAP. In addition, depending on the safety and efficacy data generated in the ATHOS 3 Phase 3 trial, LJPC-501 may provide comparable efficacy in raising MAP to existing third-line options with a better tolerability profile and lower risk of mortality. The data from the trial will play an important role in shaping where LJPC-501 would be used in the current treatment paradigm for distributive shock. If approved, LJPC-501 may be well-positioned to address the pressing need for novel vasopressors.

**Reductions in Mortality and Length of Stay Could Increase Use Ahead of Existing Third-Line Agents.** The Phase 3 trial for LJPC-501 includes secondary endpoints on the impact of LJPC-501 on mortality and hospital length of stay (LOS). Positive effects on either of these endpoints would likely drive broader formulary access and greater physician use, particularly ahead of third-line agents following failure of an initial catecholamine dose. In particular, a reduction in the LOS would have a meaningful impact on healthcare expenditure for these patients and would provide a pharmacoeconomic rationale for greater reliance on LJPC-501 instead of other agents once an initial catecholamine dose is determined to be inadequate. Due to the larger patient numbers, there is the potential for expanded use if either of these endpoints is met.

**Pricing Will Play Key Role in Shaping Formulary Access for New Agents.** We expect La Jolla to price LJPC-501, if approved, at a premium to vasopressin. How large a premium will be dictated by the overall quality of the Phase 3 safety and efficacy data and whether or not a benefit is seen on the mortality rate or length of hospital stays.
in the trial. Pricing will also be an important determinant of formulary access and restrictions by line of therapy. The trial is designed to test use of LJPC-501 as an adjunctive therapy in the last-line setting (in combination with high dose catecholamines and vasopressin) as well as ahead of vasopressin (in combination with high dose catecholamines). If the drug is approved, pricing will play an important role in shaping how broadly LJPC-501 is used in the third-line setting ahead of vasopressin or high dose catecholamines and whether any formulary restrictions are placed on the drug.

Payments for the treatment of hypotensive crises are typically made through a diagnosis-related group (DRG) reimbursement system. Overall DRG payments for CRH patients can range from $19,000 to $203,000 with a roughly $70,000 payment average. The exact drug price for LJPC-501, if approved, is not likely to meaningfully alter the overall cost of treatment for CRH patients. Many hospital-based drugs reimbursed under DRGs exceed $10,000 per course of treatment, reflecting the high price points supported in the hospital setting.

**LJPC-401: A Synthetic Formulation of Human Hepcidin for Iron Overload**

La Jolla Pharmaceutical Company is developing a synthetic form of human hepcidin, known as LJPC-401, for the treatment of iron overload. This condition is caused by genetic disorders or frequent blood transfusions, and results in the accumulation of iron in the heart, liver, and other vital organs. Excess iron promotes the generation of free oxygen radicals, which triggers tissue damage and can lead to organ failure and death. The Centers for Disease Control and Prevention (CDC) estimate that over one million patients in the US experience iron overload each year. Current treatment protocols focus on iron reduction strategies using phlebotomy or iron chelators, but many patients are intolerant or fail to improve with these therapies. In 2014, La Jolla entered an exclusive worldwide license agreement with Open Innovation Inserm Transfert, the technology transfer arm of the French public research institute Inserm, to develop LJPC-401 for the treatment of iron overload. La Jolla has completed a Phase 1 study, which demonstrated that LJPC-401 was well-tolerated and effective at lowering serum iron levels. The Company has reached an agreement with the EMA on the design of a pivotal study for LJPC-401 in patients with beta thalassemia and expects to initiate this study in the middle of 2017. The Company has received Orphan Drug designation from the EMA for LJPC-401 in the beta thalassemia indication and has also received a positive recommendation for Orphan designation for sickle cell disease (SCD).

**Mechanism of Action.** LJPC-401 is designed to reduce iron levels in the body by acting as a synthetic mimic of human hepcidin. Iron absorption is influenced by erythropoietic demand for iron, tissue oxygenation, and the body's iron stores. As shown in Figure 16, hepcidin is produced by hepatocytes in the liver and is a key iron-regulating peptide. Its release is modulated by hypoxia and iron levels. Once in circulation, hepcidin binds to the iron exporter ferroportin (FPN) on the surface of intestinal cells and macrophages. This interaction triggers FPN internalization.

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and degradation, which inhibits intestinal iron absorption. Hepcidin also blocks the release of iron from hepatic stores and macrophage-dependent recycling of red blood cells.\textsuperscript{28}

**Figure 16. Hepcidin Inhibits Iron Absorption and Recycling**

![Diagram showing iron deficiency and iron loading](source: Utzschneider et al., 2010\textsuperscript{29})

**Preclinical Studies with Synthetic Human Hepcidin**

A series of experiments conducted by investigators at the University of California, Los Angeles demonstrated that synthetic hepcidin regulates iron levels in rodents.\textsuperscript{30} The preclinical data discussed below substantiates La Jolla’s current clinical investigation of LJPC-401 in hereditary hemochromatosis and acquired iron overload.

**Figure 17** shows the systemic administration of synthetic hepcidin reduces serum iron. In the first set of experiments, animals were injected with three doses of the synthetic peptide and their serum iron concentration was measured at a defined time point. Animals receiving the highest dose of hepcidin exhibited an 80% ($p=0.03$) reduction in serum iron levels. A strong correlation was observed between dose and serum iron levels ($R = -0.0929$, $p<0.001$), suggesting that synthetic hepcidin modulates iron availability in a dose-dependent manner.

\begin{itemize}
  \item \textsuperscript{29} Utzschneider, K et al., 2010. Hereditary hemochromatosis and diabetes mellitus: implications for clinical practice. *Nature Reviews Endocrinology*, 6, pp23-33.
  \item \textsuperscript{30} Rivera, S. et al., 2005. Synthetic hepcidin causes rapid dose-dependent hypoferremia and is concentrated in ferroportin-containing organs. *Blood*, 106(6), pp2196-2199.
\end{itemize}
Hepcidin regulates serum iron by binding and inducing degradation of the exporter FPN. To demonstrate that synthetic hepcidin functions in the same manner, the investigators created several mutant synthetic peptides, labeled as hHep-20 and hHep-22 in Figure 18, and tested their ability to regulate serum iron. The mutants peptides were truncated, which could affect FPN binding. In contrast to the wild type peptide, hHep25, the mutant forms failed to reduce serum iron levels. hHep25 significantly reduced serum iron by approximately 4-fold ($p=0.001$), while hHep-20 and hHep-22 had no significant effect. Therefore, synthetic hepcidin, like the natural peptide, physically interacts with FPN to regulate iron availability.

Having demonstrated that synthetic peptide can modulate serum iron levels, the investigators next determined the pharmacokinetics of synthetic hepcidin in rodents. Serum iron levels were measured at several time points after injecting animals with a single dose of peptide. Figure 19 shows that 1 hour following injection, there was an approximately 5-fold reduction in serum iron ($p<0.001$), which was maintained for at least 48 hours. Serum iron levels recovered approximately 96 hours following administration. These data indicate that synthetic hepcidin induces a rapid
and sustained reduction of serum iron in mice, and warrants further exploration of its therapeutic potential in a clinical trial.

Figure 19. Hepcidin Causes a Rapid and Sustained Decrease in Serum Iron.

Iron Overload Disorders

Iron overload disorders are a cluster of genetic or acquired conditions that result in the excess accumulation of iron in the body. Excess iron is toxic to cells and can cause permanent tissue damage that can lead to organ failure if untreated. The Centers for Disease Control and Prevention (CDC) estimate that over one million individuals in the US experience some form of iron overload each year. The condition is most prevalent in individuals of European descent and affects men more often than women. Patients with iron overload are at an increased risk for developing liver, pancreatic, and heart disease due to the buildup of iron deposits in the organs that can lead to organ failure and death. Current treatment protocols focus on iron reduction strategies using phlebotomy or iron chelators, although some patients are intolerant or fail to improve with these therapies. There is an unmet need for an effective therapy for patients who are refractory to conventional iron overload treatments.

Molecular Basis and Pathogenesis. Iron overload is caused by an inherited disorder called hereditary hemochromatosis (HH) or is acquired in patients with certain conditions that need frequent blood transfusions. Hemochromatosis is a genetic disorder that causes the body to absorb too much iron from the diet. The most common

31 http://www.cdc.gov/ncbddd/hemochromatosis/index.html
32 Bring, P. et al., 2008. Iron Overload Disorders: Treatment Options for Patients Refractory to or Intolerant of Phlebotomy. Reviews of Therapeutics, 28(3), pp331–342
type of hemochromatosis presents in adulthood and is caused by mutations in the human hemochromatosis gene (HFE). The HFE protein regulates the absorption of iron by controlling the production hepcidin. Patients with mutations in HFE do not produce enough hepcidin, and as a result, absorb too much iron. Hemochromatosis is the major cause of iron overload in the US.

Patients who require frequent blood transfusions are also at risk of developing iron overload. Patients with severe anemia, thalassemia, sickle cell disease (SCD), or myelodysplastic syndrome (MDS) require frequent blood transfusions to supply healthy red blood cells, which deliver oxygen to the body. However, a single unit of blood contains 250 times more iron than the body’s daily metabolic requirement. Since the body is unable to effectively secrete iron through the urine, transfusion patients accumulate a large excess of iron that cannot be stored in the liver. After as few as 10 blood transfusions, the signs and symptoms of iron overload can emerge. This is known as acquired iron overload. Some of the conditions that lead to secondary iron overload are shown in Figure 20.

**Figure 20. Common Causes of Secondary Iron Overload**

<table>
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<tr>
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<td>Sickle-cell anemia</td>
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<td>Pyruvate kinase deficiency</td>
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<td>Diamond-Blackfan anemia</td>
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<td>Hereditary spherocytosis</td>
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<td>X-linked sideroblastic anemia (ALAS2 deficiency)</td>
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<tr>
<td><strong>Acquired Disorders</strong></td>
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<tr>
<td>Acquired idiopathic sideroblastic anemia (AISA)</td>
<td>Acquired</td>
</tr>
<tr>
<td>Myelodysplastic syndromes (MDS)</td>
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<tr>
<td>Myelofibrosis</td>
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<tr>
<td>Intractable aplastic anemia</td>
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<td><strong>Other</strong></td>
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<tr>
<td>Oral Iron Overloading</td>
<td>Acquired</td>
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</tbody>
</table>

*Source: LifeSci Capital*

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Beta thalassemia is also associated with low levels of endogenous hepcidin, which can contribute to elevated levels of iron absorption. Ineffective production of red blood cells in beta thalassemia is thought to lead to several compensatory mechanisms, including the suppression of hepcidin and consequently increased iron uptake. Several studies have suggested a similar process in MDS.

**Symptoms and Diagnosis.** Signs of iron overload vary based on the severity of the condition. Early symptoms of the disease include joint pain, fatigue, general weakness, unexplained weight loss, and stomach pain. Later signs can include arthritis, liver disease, diabetes, heart abnormalities, and skin discoloration, reflecting greater degrees of iron deposition in the organs. Hereditary hemochromatosis is thought to be underdiagnosed despite the availability of simple and inexpensive tests.

Iron overload is diagnosed using simple blood analysis and genetic testing. The transferrin saturation blood test measures the ratio of serum iron and total iron-binding capacity, and informs a clinician how much serum iron is actually bound to the transferrin protein. Patients with transferrin saturation greater than 45% are diagnosed with iron overload. If the patient does not have a history of frequent blood transfusions, genetic screening for mutations to the HFE gene is performed, which can provide a definitive diagnosis of hereditary hemochromatosis.

**Treatment.** Phlebotomy is an effective means of removing iron from the body and is used in patients with hereditary hemochromatosis. The frequency of phlebotomy needs to be individualized for each patient and can vary from once a month to twice-weekly for severe cases. Heavy patient burden can create problems with treatment compliance.

Individuals with secondary iron overload typically suffer from acquired or inherited anemia and thus cannot be treated with phlebotomy. Iron chelators, which are designed to specifically bind and remove iron from the blood, are the standard of care for these patients. As shown in Figure 21, there are just three chelators approved for use in patients with secondary iron overload. Iron chelators can reduce serum iron levels, but do not address the underlying disease pathology. They can also cause kidney failure, liver failure, and gastrointestinal hemorrhage.

**Figure 21. Approved Treatments for Iron Overload**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Target</th>
<th>Approved</th>
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<tbody>
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<td>deferoxamine</td>
<td>Generic</td>
<td>Iron</td>
<td>1968</td>
</tr>
<tr>
<td>Exjade/Jadenu</td>
<td>Novartis</td>
<td>Iron</td>
<td>2005</td>
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<tr>
<td>(deferasirox)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferriprox (deferiprone)</td>
<td>Apotex</td>
<td>Iron</td>
<td>2011</td>
</tr>
</tbody>
</table>

*Source: LifeSci Capital*


Deferoxamine (DFO) has been in widespread clinical use since the late 1970s and has provided evidence that chelation is an effective therapy. DFO is a hexadentate chelator with a high and selective affinity for iron. The drug is administered as long infusions because the plasma half-life is short and it is not orally bioavailable. The second approved drug for iron overload is Exjade (deferasirox) from Novartis (NYSE: NVS). The drug is an oral iron chelator developed specifically for the treatment of transfusion-dependent iron overload and non-transfusion-dependent thalassemia. The plasma half-life of 8 to 16 hours allows convenient once-daily dosing, however the drug must be taken on an empty stomach. In March 2015, Novartis introduced an improved formulation of deferasirox called Jadenu that can be taken with or without food. Although effective at managing iron overload, the above chelators are associated with serious liver and kidney toxicities, and the prescribing labels contain boxed warnings regarding the risk of renal failure, liver failure, and gastrointestinal hemorrhage. These risks indicate a clear need for safer alternatives to manage iron overload. La Jolla’s LJPC-401 could fit into this treatment landscape, if approved, as an add-on therapy for patients that don’t respond to an initial chelator doses or cannot tolerate higher doses.

Market Information

Each year, there are over one million cases of iron overload in the US, reflecting a large market of patients requiring iron reduction therapy. Roughly 250,000 cases of iron overload are due to hereditary hemochromatosis, the most common genetic disorder in Caucasians. The Company estimates that roughly 5% of patients with hemochromatosis are intolerant or fail to respond to phlebotomy. Figure 22 highlights the prevalence of certain acquired iron overload disorders in the US and Europe. Each of these indications has a low prevalence that qualifies as an orphan indication.

![Figure 22. Prevalence of Certain Acquired Iron Overload Disorders](image)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence US</th>
<th>Prevalence Europe</th>
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<tbody>
<tr>
<td>Beta Thalassemia</td>
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<td>15,000</td>
</tr>
<tr>
<td>Sickle Cell Disease</td>
<td>90,000(^{42})</td>
<td>120,000</td>
</tr>
<tr>
<td>Myelodysplastic Syndrome</td>
<td>60,000(^{43})</td>
<td>40,000(^{44})</td>
</tr>
</tbody>
</table>

Source: LifeSci Capital

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41 http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021882s010lbl.pdf


Roughly 50% of patients are intolerant or fail to respond to iron chelation therapy, creating a large market opportunity in the US for a novel treatment for iron overload. The scale of this market is highlighted by the nearly $1 billion in 2015 sales for the iron chelator Exjade. If LJPC-401 is found to be well-tolerated and effective, patients currently receiving Exjade/Jadenu or phlebotomy may opt for a safer or less invasive treatment.

In Europe, La Jolla is initially testing LJPC-401 in the beta thalassemia indication, for which the company has received Orphan Drug designation from the EMA. The Company expects to initiate a Phase 2 trial in the middle of 2017. Demonstration of safety and efficacy in the beta thalassemia patient population would allow for La Jolla to pursue additional iron overload indications such as sickle cell disease (SCD) and myelodysplastic syndrome (MDS).

LJPC-401 Clinical Data Discussion

La Jolla has conducted a Phase 1 study evaluating LJPC-401 in patients with iron overload and has reached an agreement with the European Medicines Agency (EMA) on the design of a pivotal Phase 2 trial for patients with beta thalassemia. The Company expects to launch this trial in the middle of 2017.

Phase 1 Trial

La Jolla conducted an open-label Phase 1 dose-escalation trial to study the safety and tolerability of LJPC-401 in patients with iron overload, including hereditary hemochromatosis (HH), thalassemia, and sickle cell disease (SCD). The trial demonstrated that LJPC-401 could be safely administered to patients with iron overload in order to reduce serum iron levels. The iron lowering effects of LJPC-401 appeared to be durable with the effects persisting through the 7-day observation period of the trial.

Phase 1 Trial Design. This open-label Phase 1 dose-escalation study evaluated LJPC-401 as a potential treatment for iron overload in 15 patients. Enrolled subjects received a single subcutaneous dose of LJPC-401 and were then evaluated during a 7-day observation period. The trial tested 1, 3, 10, and 20 mg of LJPC-401. The primary endpoint was safety and tolerability, including treatment-emergent adverse events (TEAEs), changes in clinical lab values, electrocardiogram (ECG), vital signs, and physical examination. The secondary endpoint was serum iron levels.

Trial Results. Overall, LJPC-401 was well-tolerated, and no dose-limiting toxicities were observed in the study. One serious adverse event (SAE) was reported in the study, which was unrelated to the study drug, and there were 9 injection site reactions that were mild-to-moderate in severity. In addition, there were no substantial changes in serum chemistries or hematology, aside from the expected changes in iron levels.

In terms of efficacy, there was a statistically significant, dose-dependent reduction in serum iron levels following treatment with LJPC-401. This result is shown in Figure 23. When treated with 20 mg of LJPC-401, subjects experienced a 58.1% reduction in serum iron levels. The peak effect was observed 8 hours after dosing with LJPC-401, and the reductions were maintained through the 7-day observation period.
**Competitive Landscape**

Most cases of iron overload can be treated with phlebotomy, although patient compliance is an issue since the procedure requires frequent trips to the clinic. Additionally, an estimated 5% of patients are intolerant or fail to respond to this procedure. Intolerance can be due to side effects such as hypotension, anemia, or inflammation of the veins used to remove blood. *Exjade* and *Jadenu* are effective oral treatments for iron overload, but they can cause severe kidney and liver toxicities. Despite the safety issues, sales of *Exjade* were $917 million in 2015, which highlights the large market opportunity for effective alternatives to phlebotomy. Since LJPC-401 is a synthetic version of a naturally-occurring signaling peptide, it may have a better safety profile. If approved, it could be used to treat those patients who are intolerant to phlebotomy or wish to avoid the potential toxicities associated with currently available iron chelators.

La Jolla is pursuing an initial indication of beta thalassemia for LJPC-401 in the EU and has reached an agreement with the EMA on the design of a pivotal trial, which is expected to launch in the middle of 2017. The Company is still evaluating the best regulatory path forward in the US to establish a broad iron overload indication for LJPC-401.

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LJPC-30S for Gram-negative Bacterial Infections and Rare Genetic Diseases

LJPC-30Sa and LJPC-30Sb are derivatives of gentamicin being developed by La Jolla to treat severe bacterial infections and rare genetic disorders. Gentamicin is an FDA-approved aminoglycoside antibiotic for gram-negative bacterial infections. The use of gentamicin has increased over the last 10 years due to its broad-spectrum activity against antibiotic-resistant bacteria. More than 3 million vials were used in the US in 2015. Despite the wide use of gentamicin, the label contains a boxed warning regarding kidney toxicity and ototoxicity. La Jolla’s gentamicin derivatives are intended to retain the therapeutic activity while minimizing dose limiting side effects. This type of product profile could be useful in treating bacterial infections, and may also have applications to rare genetic diseases via effects on mutant protein translation.

In May 2015, La Jolla announced an exclusive option agreement to acquire the Indiana University Research and Technology Center’s (IURTC) intellectual property rights covering next-generation gentamicin derivatives LJPC-30Sa and LJPC-30Sb. The Company plans to develop these compounds for bacterial infections. La Jolla also made a second agreement with IURTC and the University of Alabama, Birmingham to develop the derivatives for rare genetic disorders including cystic fibrosis and Duchenne muscular dystrophy (DMD). Following a pre-IND meeting with the FDA, La Jolla has received positive feedback on a proposed Phase 1 trial design.

Antimicrobial Activity and Safety of Gentamicin. Gentamicin is produced through a fermentation process and consists of a mixture of distinct but closely related chemical entities. Through sophisticated purification methods, it may be possible to purify chemical species that retain antimicrobial properties but do not produce human toxicities. La Jolla has purified next-generation gentamicin derivatives and examined them for antimicrobial activity and safety. The top panel of Figure 24 demonstrates that the gentamicin derivatives retain the same antimicrobial activity as their parent compound. Both gentamicin and its derivative are able to kill or inhibit growth of bacterial species B. subtilis and K. pneumoniae. The bottom panel in Figure 24 shows gentamicin and its derivative contribute differentially to kidney toxicity as measured by serum creatinine in a rodent model. Serum creatinine increased during 6 days of treatment with gentamicin but remained stable with the next-generation derivatives. The data suggest that gentamicin’s toxicity is associated with some but not all of its constituent chemical entities. A gentamicin derivative that retains antimicrobial activity but has reduced kidney toxicity would represent a major advance for patients.
Figure 24. Derivatives Maintain Antimicrobial Activity without Toxicity

Source: Company Presentation

**Mechanism for Gentamicin in Rare Genetic Diseases.** Gentamicin kills bacterial cells by binding the ribosome and blocking translation of messenger RNAs (mRNAs) into proteins. At low doses, gentamicin has minimal impact on human ribosomes. At higher doses, it interacts with the human ribosome and modulates its translation specificity. One important outcome of this alteration is the ability of high dose gentamicin cells to act as a suppressor of premature termination codons. This is referred to as read-through activity and has applications in certain rare genetic disorders where incorrectly positioned stop codons prevent the production of full-length, functional proteins. A percentage of well-known rare diseases such as DMD and cystic fibrosis are due to premature stop codons. Preclinical work has validated gentamicin’s ability to induce read through in models of these diseases.46,47

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Market Information

Despite its safety profile, gentamicin is one of the most commonly prescribed hospital antibiotics worldwide. It is the most commonly prescribed aminoglycoside in the US and accounted for approximately two-thirds of the six million vials sold in 2015. The Company estimates that 2015 sales of gentamicin exceeded $500 million. If LJPC-30S is demonstrated to be safe and effective, it may capture a larger percentage of the existing aminoglycoside market and/or expand gentamicin’s current market into new indications where concerns over toxicity prevents its use. The IP protection optioned from Indiana University and University of Alabama, Birmingham will provide the Company with market protection beyond 2026.

Intellectual Property

La Jolla’s intellectual property portfolio is shown in Figure 25. For LJPC-501, La Jolla has issued patents that cover the product to 2034.

Figure 25. La Jolla’s Intellectual Property Portfolio

<table>
<thead>
<tr>
<th>Description</th>
<th>United States</th>
<th>Ex-US</th>
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<tr>
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<td>2</td>
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</tbody>
</table>

Source: Company Reports

Management Team

George F. Tidmarsh, M.D., Ph.D.
President/CEO/Secretary

Dr. Tidmarsh has been President, Chief Executive Officer, Secretary and a Director of La Jolla since January 2012. Dr. Tidmarsh has over 25 years of experience in biotechnology, including the successful clinical development of three FDA-approved drugs. Prior to joining La Jolla, he served as the Chief Executive Officer of Horizon Pharma, Inc., a company he founded in 2005. While at Horizon, he led all aspects of development of Duexis, which was approved by the FDA for the treatment of rheumatoid arthritis. He also founded Threshold Pharmaceuticals, Inc. and held senior positions at Coulter Pharmaceutical, Inc. (acquired by GlaxoSmithKline) and SEQUUS Pharmaceuticals, Inc. (acquired by Johnson & Johnson). While at Coulter and SEQUUS, Dr. Tidmarsh led the clinical development of
BEXXAR and Doxil, respectively, two FDA-approved anti-cancer agents. Dr. Tidmarsh received his M.D. and Ph.D. from Stanford University, where he also completed fellowship training in Pediatric Oncology and Neonatology and remains a Consulting Professor of Pediatrics and Neonatology.

Lakhmir S. Chawla, MD
Chief Medical Officer

Dr. Chawla joined La Jolla as Chief Medical Officer, effective July 1, 2015. Previously, Dr. Chawla was a Professor of Medicine at the George Washington University, where he had dual appointments in the Department of Anesthesiology and Critical Care Medicine and in the Department of Medicine, Division of Renal Diseases and Hypertension. Dr. Chawla was also the Chief of the Division of Intensive Care Medicine at the Washington D.C. Veterans Affairs Medical Center. During his tenure at George Washington, Dr. Chawla was the designer and lead investigator of a pilot study called the ATHOS (Angiotensin II for the Treatment of High Output Shock) trial. Data from the ATHOS trial was published in the medical journal Critical Care during 2014 and demonstrated the utility of angiotensin II in patients with severe shock. These data were also used in support of the initiation of La Jolla’s ATHOS 3 trial, a Phase 3 clinical trial of LJPC-501, La Jolla’s proprietary formulation of angiotensin II, for the treatment of catecholamine-resistant hypotension, which was initiated in March 2015. Dr. Chawla is an internationally renowned expert in the field of acute kidney injury (AKI) and was an active investigator in the fields of inflammation and AKI, AKI biomarkers, AKI risk prediction, chronic kidney disease caused by AKI and AKI therapeutics. In addition, Dr. Chawla was an active investigator in shock, inflammation and extracorporeal therapies, including: continuous renal replacement therapy, dialysis and albumin dialysis. Dr. Chawla is also the author of over 100 peer-reviewed publications and was previously an Associate Editor for the Clinical Journal of the American Society of Nephrology.

Dennis M. Mulroy
Chief Financial Officer

Mr. Mulroy has been the Chief Financial Officer of La Jolla since April 2015. Prior to joining La Jolla, Mr. Mulroy served as Chief Financial Officer of Taxus Cardium Pharmaceuticals Group Inc., a publicly traded biotechnology company, since 2005. Prior to joining Taxus Cardium, Mr. Mulroy served as Chief Financial Officer of Molecular Imaging, Inc. and SeraCare Life Sciences, Inc., and held financial management positions of increasing responsibility at several other companies. Mr. Mulroy began his career as a Certified Public Accountant with Ernst & Young LLP in San Diego and holds a degree in Business Administration, with an emphasis in Accounting, from the University of San Diego.

Jennifer A. Carver, MBA
Chief Operating Officer

Ms. Carver has held the position of Senior VP of Operations for La Jolla since January 2016 and has broad operational responsibility for business development, clinical operations, regulatory affairs, pharmaceutical operations, legal operations, project management, information technology, and quality. She joined La Jolla in February 2014 as Sr. Director of Project Management with the purpose of establishing a project team structure for the rapidly growing company. Ms. Carver was promoted to VP of Project Management in December 2014 and then promoted to VP of Operations in June 2015. Ms. Carver has over 20 years of experience in the healthcare industry and with experienced cross-functional leadership in pharmaceutical drug development from early development through commercialization. Prior to joining La Jolla, Ms. Carver was Senior Director of Project Management at Spectrum Pharmaceuticals, Inc.,
leading the NDA and launch activities for Beleodaq, an FDA-approved anti-cancer agent. Previously, she held various roles at Allos Therapeutics, Inc., including project manager for Folotyn, an FDA-approved anti-cancer agent, and leading integration activities following the acquisition of Allos by Spectrum Pharmaceuticals in 2012. Ms. Carver earned her B.S.N. and M.B.A. from the University of Colorado.

James M. Rolke  
*Chief Scientific Officer*

Mr. Rolke has been the Vice President of Research & Development of La Jolla since January 2012. Mr. Rolke has over 20 years of experience in the biotechnology industry. Prior to joining La Jolla, Mr. Rolke held several key positions at biotechnology companies, including Chief Technology Officer at Pluromed, Inc. (acquired by Sanofi), Director of Operations at Prospect Therapeutics, Inc., Associate Director of Pharmaceutical Development at Mersana Therapeutics, Inc., Manager of Process Development at GlycoGenesys, Inc., Principal Scientist at Surgical Sealants, Inc., Scientist at GelTex, Inc., and Associate Scientist at Alpha-Beta Technology, Inc. Mr. Rolke received his B.S. in chemistry from Keene State College.

Jeffrey J. Jensen  
*Vice President of Global Clinical Operations*

Mr. Jensen joined La Jolla in March of 2016 as Vice President of Global Clinical Operations. He has over 30 years of experience in drug development at biotech, pharmaceutical and contract research companies in the US and Europe. Previously he was a Vice President of Clinical Operations and Clinical Lead at Pfizer, and held senior positions at Thesan, Metabasis, Excaliard, Quintiles, PPD, and INC Research. He specializes in managing global teams across several therapeutic areas and leading partnerships with research investigators and contract research organizations.

James A. Wilkie  
*Vice President of New Enterprise Development*

Mr. Wilkie has been the Vice President of Pharmaceutical Operations of La Jolla since July 2014. Mr. Wilkie has over 29 years of experience in the life sciences industry. Prior to joining La Jolla, Mr. Wilkie served as Chief Operating Officer of Pluromed, Inc., until the sale of the company in 2012 to Genzyme Corporation. Mr. Wilkie joined Pluromed as Vice President of Operations in 2005 and was the first employee. He led the development team to commercialize two successful products in the U.S. and Europe, where he was responsible for the overall operation, including product development, clinical affairs, RA/QA, manufacturing, distribution and administration. Prior to his experience at Pluromed, Mr. Wilkie held various positions of increasing responsibility at MedChem Products, Inc., including Director of Engineering for 3 sites. Upon the sale of MedChem to C. R. Bard, he spun-off certain technology and co-founded Surgical Sealants, Inc. He holds 2 issued patents and several pending applications. Mr. Wilkie received his B.S. in Engineering from the University of Massachusetts.
Risk to Investment

We consider an investment in La Jolla Pharmaceutical Company to be a high-risk investment. LJPC currently has no marketed products and is pursuing the clinical development and marketing approval of LJPC-501 and LJPC-401. Additionally, as a developmental-stage biotechnology company, LJPC is not profitable and may have insufficient funds to complete the development and commercialization of their products. LJPC may need to seek additional financing from the public markets, which may result in dilution to existing shareholders and negatively impact LJPC’s stock price.
Analyst Certification

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