ZS Pharma (ZSPH)

ZS-9 vs. Patiromer: A Side by Side Comparison

ZS Pharma (ZSPH) and Relypsa (RLYP) are each developing an agent for the treatment of excess serum potassium, known as hyperkalemia, which affects an estimated 4 million individuals in the US. As the companies near expected FDA approval and commercialization, we review some key data outlining why ZS-9 should have a significant commercial advantage over patiromer.

- **ZS-9 Could Capture a Large Fraction of the Estimated $3-5 Billion Hyperkalemia Market.** Hyperkalemia occurs frequently in patients with chronic kidney disease (CKD), diabetes, and heart failure (HF), which all have a high and increasing prevalence worldwide. Hyperkalemia can also arise from the use of RAAS inhibitors, which have a demonstrated cardio-renal protective effect, yet cause the kidney to retain potassium and thereby increase serum potassium levels. There are over 2.8 million chronically hyperkalemic patients with late-stage CKD and/or heart failure in the US. The market potential for the treatment of hyperkalemia in CKD and heart failure alone could be $3-5 billion in the US using reasonable assumptions for market penetration, treatment duration, and pricing. ZS-9 has the potential to capture a large share of this market, which can be addressed with a specialty sales force focused on nephrology and cardiology. In addition, because of ZS-9's rapid onset of action, the product is uniquely positioned to address hyperkalemia in the hospital setting, which we estimate to be $200-250 million at branded prices based on current SPS sales.

- **ZS-9 Is the Clear Winner.** ZS Pharma and Relypsa have collected extensive clinical data supporting the use of their respective agents as treatments for hyperkalemia and FDA approval of both agents is widely expected. The data will likely support a label for the acute reduction and long-term maintenance of serum potassium (K^+). There is little doubt regarding the advantages of ZS-9 and patiromer over the current standard of care, but which agent will be preferred by patients and physicians? Relypsa submitted an NDA for patiromer in October 2014 and has a PDUFA date of October 21, 2015. ZS Pharma expects to submit an NDA for ZS-9 in the first half of 2015. Despite the modest head start by Relypsa, there are several features of ZS-9 that distinguish it from patiromer and should help it become the standard of care. These advantages could allow ZS-9 to capture a substantial portion of the $5-7 billion hyperkalemia market.

Expected Upcoming Milestones

- H1 2015 – Expected NDA & MAA submission for ZS-9 for the treatment of hyperkalemia.
- 2015 – Potential updates from long-term studies ZS004e and ZS005.
- H1 2016 – Potential approval and commercial launch of ZS-9.

Analysts

Jerry Isaacson, Ph.D. (AC)
(646) 597-6991
jisaacson@lifescicapital.com

Market Data

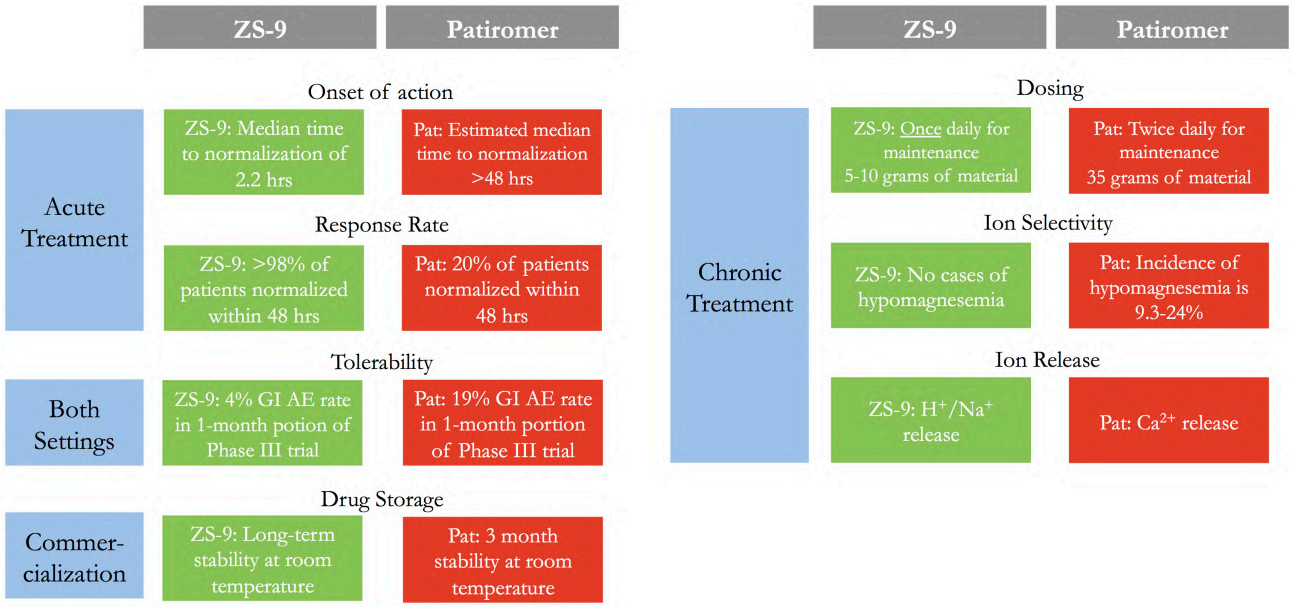
Price	$47.69
Market Cap (M)	$993
EV (M)	$881
Shares Outstanding (M)	20.8
Fully Diluted Shares (M)	25.5
Avg Daily Vol	209,354
52-week Range:	$25.51 - $52.80
Cash (M)	$121.5
Net Cash/Share	$5.36
Annualized Cash Burn (M)	$40.0
Years of Cash Left	3.0
Debt (M)	$10.0
Short Interest (M)	1.95
Short Interest (% of Float)	15.8%

Financials

FY Dec		2013A	2014A
EPS	Q1	NA	NA
	Q2	(4.81)A	(4.72)A
	Q3	(6.14)A	(0.81)A
	Q4	NA	NA
	FY	NA	NA

- **Advantages of ZS-9 over Patiromer.** There are several key features of ZS-9 that could position it ahead of patiromer in the acute and chronic settings. **Figure 1** lists several drug qualities and how the two agents compare regarding: acute treatment, chronic treatment, both treatment settings, and potential commercialization. The advantages of ZS-9 include faster onset of action, higher response rate, more convenient dosing, ion-specific binding, greater tolerability profile, lack of Ca^{2+} as a counter-ion, and simpler drug distribution and storage. A detailed description of each drug quality is below the table.

Figure 1. Advantages of ZS-9 over Patiromer



Source: LifeSci Capital

- **Onset of action.** This is a very important feature, particularly for patients with dangerously high levels of potassium. In Phase III, ZS-9 led to a statistically significant reduction in serum potassium after only 1 hour, and was able to normalize K^+ in a median time of 2.2 hours.[1] Patiromer takes 7 hours to produce its first statistically significantly change in serum K^+ based on data from a Phase I onset of action study.[2] This is expected for patiromer as an agent that binds K^+ in the colon. The median time to normalization for patiromer has not been calculated or disclosed, although it is longer than 48 hours based on the Phase I study. 76% of patients were normalized at week 4 in Relypsa's Phase III trial,[3] suggesting that the median time to normalization is less than 4 weeks. The delay relative to ZS-9 in reducing K^+ levels is a disadvantage for patiromer, and this fact alone may make ZS-9 the preferred agent regardless of setting.

  One underappreciated commercial advantage of treating hyperkalemia in the hospital setting is that many of these patients will require long-term therapy to manage their disease. An estimated 50% of all chronic hyperkalemia diagnoses are made in the hospital setting. Many of the same physicians who prescribe inside of a hospital, such as nephrologists and cardiologists, also see patients outside the hospital. They will be more likely to prescribe a product they successfully employed in the acute setting.

- **Response Rates.** Consistent with a rapid onset of action, ZS-9 can normalize >98% of patients' serum K^+ within 48 hours of treatment.[4] Normokalemia is defined as a serum K^+ of 3.5-5.0 mEq/L. In contrast, 20% of patients were normalized at 48 hours in a Phase I patiromer onset of action study, and 76% were normalized at 1 month.[5] The data indicate that a greater proportion of patients will reach normokalemia with ZS-9 in a shorter time period.

  The 10 and 15 gram doses of ZS-9 are associated with increased bicarbonate levels.[6] Bicarbonate is used as a treatment for metabolic acidosis in CKD patients. Metabolic acidosis increases CKD progression and is associated with higher mortality. By significantly raising bicarbonate levels to within the normal range, especially in CKD patients, ZS-9 could improve clinical outcomes in addition to the cardiac benefits of serum potassium normalization. ZS-9 also led to reductions in aldosterone levels in

the HARMONIZE trial, which were measured as a pre-specified endpoint. Aldosterone is a hormone involved in blood pressure regulation, Na^+ reabsorption, and K^+ secretion. Potassium is the strongest stimulator of aldosterone and hyperkalemic patients can suffer from chronically elevated levels of the hormone. Dysregulated aldosterone levels can lead to cardiac and renal fibrosis. ZS-9's ability to reduce the hormone is another potential benefit of the treatment for the HF and CKD patients who will likely take the drug.

- **Dosing.** ZS-9 and patiromer are powders that are mixed with water and ingested as a suspension. The dosing schedule for ZS-9 is once-daily for the maintenance of hyperkalemia compared to twice-daily for patiromer. Relypsa is conducting a once-daily dosing study with data expected in the first half of 2016. If the data are positive, Relypsa expects a label update in the first half of 2017.

  In addition to the schedule, we are particularly focused on the total amount of patiromer ingested per day. The average dose in Relypsa's Phase III trial was reported as 21.4 grams for patients with mild to moderate disease in the withdrawal phase.[7] Each patiromer packet contains 4.2 grams of active drug, meaning that patients received on average 5 packets per day. Each packet also contains 0.8 grams of calcium as noted in Relypsa's 2013 10-K, which was included in the dosing nomenclature for earlier studies. Each packet of patiromer is given with 2 grams of sorbitol and an unknown amount of xanthan gum as excipients, bringing the total amount of material ingested from each packet to at least 7 grams. This means that patients with moderate to severe hyperkalemia received on average 35 grams of material each day, which includes 4 grams of calcium and 10 grams of sorbitol. In contrast, we estimate that 90% of patients on ZS-9 will receive 5 or 10 grams per day with a minority needing 15 grams per day or 5 grams every other day to maintain normal K^+ levels. ZS-9 is not given with any other ingredients such as sorbitol or excipients. Therefore, the dosing load for patients is substantially lower with ZS-9 in terms of frequency and total amount of drug and other material.

- **Ion selectivity.** ZS-9 is highly selective for potassium and does not trap other ions. Patiromer, in contrast, binds other ions non-specifically, including magnesium. The incidence of hypomagnesemia was 9% in a 52-week study, 8% in the 8-week randomized withdrawal phase of the Phase III study,[8] and 24% in a trial of heart failure patients (PEARL-HF).[9] This highlights the lack of selectivity for patiromer. Worth noting is that the 9% incidence of hypomagnesemia reported in the 52-week trial was determined via investigator assessment, which may not have been based on blood levels of the ion. The 8% incidence of hypomagnesemia in Relypsa's Phase III study was assessed using a cutoff of <1.4 mg/dL, which is different from the <1.8 mg/dL cutoff used in the PEARL-HF study. It is challenging to fully assess the impact of patiromer on hypomagnesemia, in part because the reported values are all derived using different methods. We believe that investigator-determined hypomagnesemia is more severe than that diagnosed via laboratory values. In trials with ZS-9 there have been zero instances of hypomagnesemia.

  Hypomagnesemia is a particularly worrisome consequence that seems to occur more frequently in patients that have treatment-induced hypokalemia, and could place those patients at risk for ventricular arrhythmias and sudden cardiac death. ZS-9 does not bind to magnesium and place patients at risk for hypomagnesemia. The risk of hypomagnesemia could result in greater monitoring requirements for patients receiving patiromer.

- **Ion Release.** Patiromer contains Ca^{2+} as a counter ion that is exchanged with H^+, Na^+, Mg^{2+}, and K^+ in the GI tract, leaving calcium behind. Increased calcium places patients in a positive calcium balance, which can lead to calcium deposition in soft tissue. The deposits can contribute to the development of heart disease. For these reasons, CKD patients are often prescribed non-calcium based phosphate binders to manage hyperphosphatemia and minimize new calcium deposition in the arteries. Although Relypsa has not detected elevations in serum Ca^{2+} from its clinical studies, serum Ca^{2+} measurements do not detect a calcium load, and a calcium balance study would need to be conducted to measure calcium deposits.

  A daily dose of patiromer contains approximately 4 grams of Ca^{2+} based on the 21.4 gram average daily dose from Relypsa's Phase III trial. The Cleveland Clinic recommends Ca^{2+} intake of 1.4-1.6 g/day, not to exceed 2 g/day, for patients with CKD. Most Ca^{2+} comes from dietary intake, and the long-term exposure to additional Ca^{2+} via patiromer may represent an issue for CKD patients, which account for the majority of hyperkalemia cases.

  ZS-9 exchanges H^+ and Na^+ for K^+. However, due to the lower dose amounts used, counter-ion load is a fraction of that caused by patiromer. Recently published data from ZS002 shows that urinary sodium excretion was no different than placebo even in patients taking 30 grams per day of ZS-9. Importantly, in long-term studies with ZS-9, including patients on drug for greater than 10 months, there have been no signs of increased sodium load or peripheral edema.

- **Tolerability.** The combined gastrointestinal (GI) adverse event rate for patiromer was 19% in the 1-month portion of Relypsa's Phase III study.[10,11] In contrast, the combined GI adverse event rate across all ZS-9 doses was 4% in the 1-month portion of ZS Pharma's most recent Phase III trial.[12] The superior tolerability profile of ZS-9 is expected to lead physicians to preferentially prescribe it, especially for chronic hyperkalemia patients.

- **Drug Storage.** ZS-9 is stable at room temperature and does not require cold temperatures during shipping or storage. Patiromer can also be stored at room temperature, but the shelf life is reduced from 12 months to only 3 months when not kept in cold storage between 2 and 8°C. The requirement for cold storage is a commercial burden for patiromer, especially when considering a global brand. Also worth noting is that based on an average daily dose of 35 grams of material, patients receiving patiromer will need over 1 kilogram (2.2 pounds) of product for a monthly supply. In contrast, a monthly supply of ZS-9 is 150-300 grams. The handling and storage of 1 kilogram of patiromer could be a burden.

- **Conclusion.** ZS Pharma's ZS-9 has several advantages over patiromer that should make it the preferred agent for treating acute and chronic hyperkalemia. The faster onset of action and ability to normalize serum K^+ levels in a greater fraction of patients alone makes ZS-9 the drug of choice. ZS-9 has superior dosing and tolerability, which is particularly important in the chronic setting. Most patients receiving ZS-9 for chronic treatment will only require a single dose of 5-10 grams per day. On the safety/tolerability side, ZS-9 does not place patients at risk for hypomagnesemia or the potential side effects associated with the long-term exposure to calcium, unlike patiromer. ZS-9 also has a better side effect profile.

---

[1] Kosiborod, M. et al., 2014. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *JAMA*, 312(21), pp2223-2233.

[2] Bushinsky, D.A. et al., 2014. Patiromer induced a rapid onset of action and sustained potassium lowering throughout the treatment period in CKD patients with hyperkalemia. *11th Global CVCT Forum*, Poster #153.

[3] Weir, M.R. et al., 2015. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *The New England Journal of Medicine.* 372(3), pp211-221.

[4] Kosiborod, M. et al., 2014. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *JAMA*, 312(21), pp2223-223

[5] Bushinsky, D.A. et al., 2014. Patiromer induced a rapid onset of action and sustained potassium lowering throughout the treatment period in CKD patients with hyperkalemia. *11th Global CVCT Forum*, Poster #153.

[6] Kosiborod, M. et al., 2014. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *JAMA*, 312(21), pp2223-2233.

[7] Weir, M.R. et al., 2015. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *The New England Journal of Medicine.* 372(3), pp211-221.

[8] Weir, M.R. et al., 2015. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *The New England Journal of Medicine.* 372(3), pp211-221.

[9] Pitt, B. et al., 2011. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *European Heart Journal*, 32, pp820-828.

[10] Weir, M.R. et al., 2015. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *The New England Journal of Medicine.* 372(3), pp211-221.

[11] Relypsa Analyst Day, January 2015.

[12] Kosiborod, M. et al., 2014. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *JAMA*, 312(21), pp2223-2233.

Analyst Certification

The research analyst denoted by an "AC" on the cover of this report certifies (or, where multiple research analysts are primarily responsible for this report, the research analyst denoted by an "AC" on the cover or within the document individually certifies), with respect to each security or subject company that the research analyst covers in this research, that: (1) all of the views expressed in this report accurately reflect his or her personal views about any and all of the subject securities or subject companies, and (2) no part of any of the research analyst's compensation was, is, or will be directly or indirectly related to the specific recommendations or views expressed by the research analyst(s) in this report.

DISCLOSURES

This research contains the views, opinions and recommendations of LifeSci Capital, LLC ("LSC") research analysts. LSC (or an affiliate) has received compensation from the subject company for producing this research report. Additionally, LSC may provide investment banking and other broker-dealer services to the subject company and may receive compensation from the subject company for such services. LSC (or an affiliate) has also provided non-investment banking securities-related services, non-securities services, and other products or services other than investment banking services to the subject company and received compensation for such services within the past 12 months.

Neither the research analyst(s), a member of the research analyst's household, nor any individual directly involved in the preparation of this report, has a financial interest in the securities of the subject company. Neither LSC nor any of its affiliates beneficially own 1% or more of any class of common equity securities of the subject company.

LSC is a member of FINRA and SIPC. Information has been obtained from sources believed to be reliable but LSC or its affiliates (LifeSci Advisors, LLC) do not warrant its completeness or accuracy except with respect to any disclosures relative to LSC and/or its affiliates and the analyst's involvement with the company that is the subject of the research. Any pricing is as of the close of market for the securities discussed, unless otherwise stated. Opinions and estimates constitute LSC's judgment as of the date of this report and are subject to change without notice. Past performance is not indicative of future results. This material is not intended as an offer or solicitation for the purchase or sale of any financial instrument. The opinions and recommendations herein do not take into account individual client circumstances, objectives, or needs and are not intended as recommendations of particular securities, companies, financial instruments or strategies to particular clients. The recipient of this report must make his/her/its own independent decisions regarding any securities or financial instruments mentioned herein. Periodic updates may be provided on companies/industries based on company specific developments or announcements, market conditions or any other publicly available information. Additional information is available upon request.