

ZS Pharma (ZSPH)

LifeSci Capital Initiates Coverage of ZS Pharma (ZSPH)

LifeSci Investment Abstract

ZS Pharma (NasdaqGM: ZSPH) is a biopharmaceutical company developing an oral, non-absorbable, highly selective ion-trap therapy to treat serious medical conditions. The Company has positive Phase II and Phase III data from their lead candidate, ZS-9, in patients with excess serum potassium, or hyperkalemia. An NDA for ZS-9 should be submitted by the first half of 2015 and launch would occur by early 2016 if approved.

Key Points of Discussion

- **ZS Pharma is Developing ZS-9 for Hyperkalemia.** Following a successful IPO in June, ZS Pharma is focused on the development of ZS-9, a novel, oral, non-absorbable, and highly selective binder that traps excess potassium in the gastrointestinal tract and facilitates its removal from the body. ZS-9 rapidly (within 1 hour) and significantly decreases serum potassium with an excellent safety/tolerability profile.
- **Positive Phase II and Phase III Studies.** ZS Pharma completed a 750 patient Phase III study (ZS003) in patients with hyperkalemia with positive results that were highly statistically significant. These data confirmed the results observed in Phase II and show that ZS-9 acts rapidly and predictably as evidenced by the high proportion of patients that whose potassium normalizes during the 48-hour treatment period. Results from an Extended Treatment Phase indicate that ZS-9 can maintain a significant potassium reduction for 12 days. In addition to significant efficacy, ZS-9 was shown to have an adverse event profile that was similar to placebo. A second Phase III study (ZS004) is fully enrolled and topline data are expected in late in the third quarter or early in the fourth quarter of this year. Full data are likely to be presented at a medical conference in the fourth quarter of 2014.
- **ZS Pharma Development Program Supports Broad Use of ZS-9.** ZS Pharma has completed two positive clinical studies of ZS-9 in patients with hyperkalemia and it was shown to have similar efficacy across populations regardless of disease etiology. Furthermore, the Company has completed enrollment in a second Phase III study (ZS004) and initiated a long term safety study (ZS005) to establish the efficacy and safety of ZS-9 in patients for extended treatment of hyperkalemia. NDA and MAA submissions are expected in the first half of 2015.

Expected Upcoming Milestones

- Late Q3 or early Q4 2014 – Topline data from ZS004 – a 1 month maintenance study with 5 month extension in patients with chronic hyperkalemia.
- H1 2015 – Expected NDA & MAA submission for ZS-9 for the treatment of hyperkalemia.

Analysts

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Market Data

Price	\$37.13
Market Cap (M)	\$773
EV (M)	\$663
Shares Outstanding (M)	20.8
Fully Diluted Shares (M)	26.8
Avg Daily Vol	165,889
52-week Range:	\$25.51 - \$43.00
Cash (M)	\$130.0
Net Cash/Share	\$5.28
Annualized Cash Burn (M)	\$40.0
Years of Cash Left	3.3
Debt (M)	\$20.0
Short Interest (M)	0.72
Short Interest (% of Float)	3.5%

Financials

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

- **Hyperkalemia is a Serious Life Threatening Condition.** Hyperkalemia causes disturbances in the cellular electrochemical gradient, which can lead to cardiac arrhythmias and sudden cardiac death. A large number of studies in different patient populations have shown that increased potassium levels are correlated with an increased risk of death. Treatment with ZS-9 could lower potassium levels and prevent return to hyperkalemia thereby lowering risk of death.
- **RAAS Inhibitors Have Proven Benefits but Increase Risk of Hyperkalemia.** Inhibitors of the renin-angiotensin-aldosterone system (RAASi), including ACEs, ARBs, and aldosterone blockers, have been proven in large outcomes studies to reduce morbidity, mortality, and progression of disease in patients with heart failure and kidney disease. However their mechanism of action results in the retention of potassium, which increases risk of hyperkalemia and often leads to discontinuation of RAASi therapy. Clinical data from the Phase II and Phase III trials indicate that ZS-9 is able to significantly reduce serum potassium in patients receiving RAASi. Administration of ZS-9 would allow patients to continue RAASi therapy and benefit from the cardio-renal protective effects without having to worry about the consequences of excess potassium.
- **Significant Market Opportunity – Could Exceed \$1 Billion.** 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 cause the kidney to retain potassium, thereby increasing serum potassium levels. There are an estimated 2.4 million late-stage CKD patients and approximately 400,000 HF patients with hyperkalemia in the US. We estimate that 1.4 million of these patients will seek treatment for their disease. We further estimate that at branded prices, the acute market, meaning use in the hospital setting, is a \$100-200 million opportunity. Further, the market for the extended treatment of hyperkalemia, or long-term maintenance of normokalemia is \$1.2 to \$1.3 billion in the US. Our estimates assume a small sales force of 100-150 individuals. The market opportunity could be much larger with an expanded sales force or under a partnership situation with a large pharmaceutical company. Hyperkalemia is also a substantial problem in Europe, Japan, and the rest of the world, which further increases the market opportunity for ZS-9.
- **ZS-9 Potential Best-in-Class.** The emerging clinical data suggests that ZS-9 may have a best-in-class profile. ZS-9 has several characteristics that give the product a potential competitive advantage:
 - High efficacy at once daily dosing.
 - Rapid onset of action, statistically significant reductions after 1 hour of the first dose.
 - Placebo-like tolerability in studies thus far.
 - It is a non-absorbable inorganic crystal.
 - Selective for potassium over other cations – no effect on other critical electrolytes.
 - Stable, with long shelf life at room temperature and no need for special handling or packaging.
 - In-house manufacturing and low cost of goods at planned doses.
- **Current Treatments for Hyperkalemia are Ineffective.** No treatments for hyperkalemia are able to effectively reduce serum potassium over the long-term. *Kayexalate*, (sodium polystyrene sulfonate or SPS) is the current standard of care treatment for acute potassium reduction, but its safety and efficacy has never been proven in randomized trials. SPS is poorly tolerated causing a high incidence of GI side effects such as nausea, vomiting, constipation, and diarrhea, which leads to poor compliance and renders the drug unsuitable for chronic use. In addition, in 2009 the FDA issued a warning for colonic necrosis that sparked a debate in the medical community on

whether SPS should ever be used.¹ For patients on RAAS inhibitors, removing RAAS medications can decrease serum potassium, but increases the risk of mortality due to uncontrolled hypertension. The need for a novel method that can safely and effectively treat hyperkalemia is clear.

- **ZS-9 is Competitive with Other Drugs in Development.** ZS-9 is able to significantly reduce serum potassium as early as 1 hour after treatment, compared to Relypsa's (RLYP) patiromer that recently demonstrated significant reductions at 7 hours post-treatment. Patiromer also takes approximately 2-3 weeks to reach maximum efficacy, whereas ZS-9 has a maximum effect by 48 hours. Phase III data indicate that potassium reduction can be maintained for up to 12 days with daily dosing of ZS-9, compared to long-term studies with patiromer that used a twice-daily dosing schedule. ZS-9 may be active in a larger fraction of patients, as all patients receiving the highest dose of ZS-9 achieved serum potassium levels below 5.0 mEq/L in a Phase II study. In Relypsa's Phase III trial, 43% of subjects returned to serum potassium levels of 5.1 mEq/L or higher at some point during 8 weeks of treatment.

Trial data indicate that ZS-9 may have a lower overall rate of AEs and gastrointestinal-related AEs than patiromer, a key consideration for an extended use product. Relypsa may have a first-to-market advantage with a slightly earlier NDA filing, although based on the dosing structure and differentiated safety profile, ZS-9 could achieve a large share of the market even with a later launch.

Financial Discussion

ZS Pharma Raised \$112 Million in Successful IPO. On June 23rd, ZS Pharma completed its IPO and is now listed on the Nasdaq Global Market exchange under ticker ZSPH. The Company sold 6.84 million shares, including the exercise of the underwriters' overallotment option, at a price of \$18.00 per share. Net proceeds from the offering were \$112 million. ZS Pharma's cash balance at the end of the second quarter 2014 was \$130 million.

Company Description

ZS Pharma is a biopharmaceutical company developing highly selective ion-trap therapies for the treatment of serious medical conditions. The Company's lead candidate, ZS-9, is an insoluble, non-absorbed zirconium silicate for the treatment of hyperkalemia, a disorder of excess potassium in the blood. ZS-9 is being developed for the treatment of both acute and chronic hyperkalemia. ZS Pharma plans to file an NDA for the treatment of hyperkalemia in the first half of 2015 and, if ZS-9 is approved, will launch the drug in 2016. ZS Pharma also has an ammonium specific crystal that will be developed for the treatment of hepatic encephalopathy and other hyperammonemia conditions. The Company completed an IPO in June 2014 raising \$112 million in net proceeds to fund operations.

ZS-9: Selective Potassium Ion-Trap for Hyperkalemia

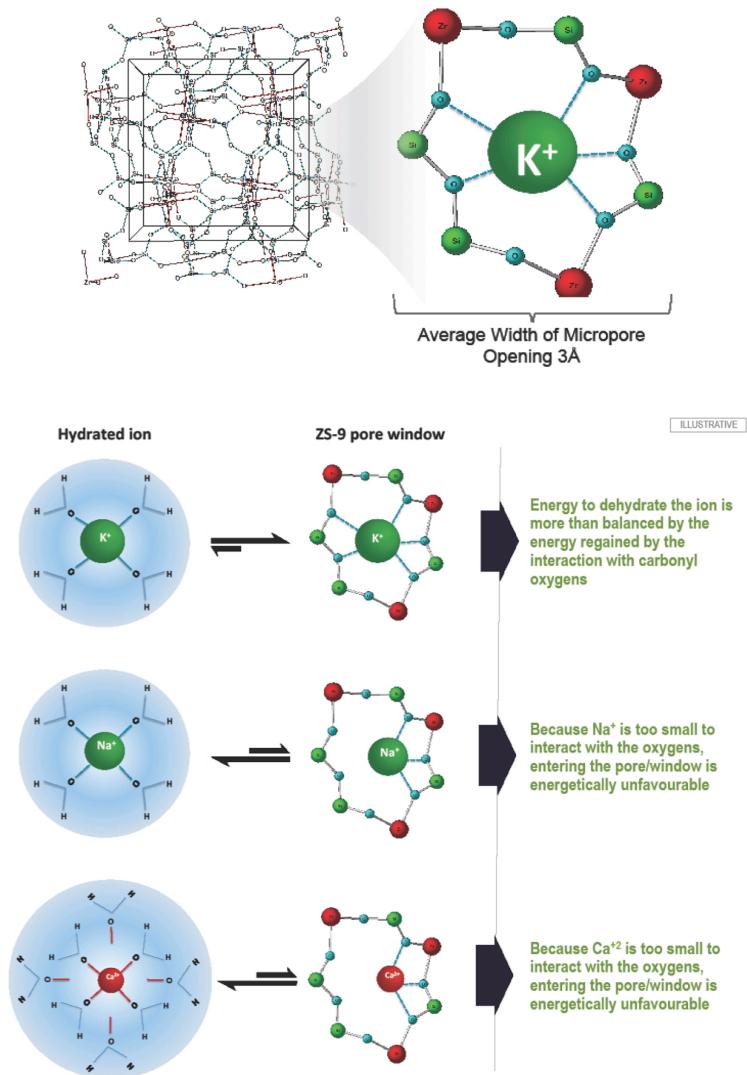
ZS-9 is an insoluble, non-absorbed zirconium silicate with a clearly defined three dimensional crystalline lattice structure that was designed and engineered to preferentially trap potassium ions. In contrast to non-selective polymer resins, the high potassium selectivity enables ZS-9 to display high *in-vitro* binding capacity even in the

¹ Stapleton, F.B., 2010. Is Kayexalate Effective for Hyperkalemia, and Is It Safe? *NEJM Journal Watch*.

presence of other ions. Head to head *in-vitro* experiments show that ZS-9 has roughly 10 times the potassium binding capacity as *Kayexalate*. This selectivity has important therapeutic consequences: ZS-9 has high potency in patients at modest dose amounts; ZS-9 exhibits a rapid onset of action by acting early in GI tract where potassium is not the most abundant ion; and ZS-9 has no effect on other important electrolytes that are critical for normal human function. In addition, ZS-9 shows high thermal stability and can be manufactured with attractive margins.

ZS-9 Crystal Structure is Specific for Potassium – Excludes Other Ions. ZS-9 is a microporous zirconium silicate compound comprised of zirconium, silicon, and oxygen atoms arranged to form cation binding pores. **Figure 1** shows an atomic depiction of the cation binding pores.²

Figure 1. Ionic Diameters and Representation of ZS-9 Binding Pore

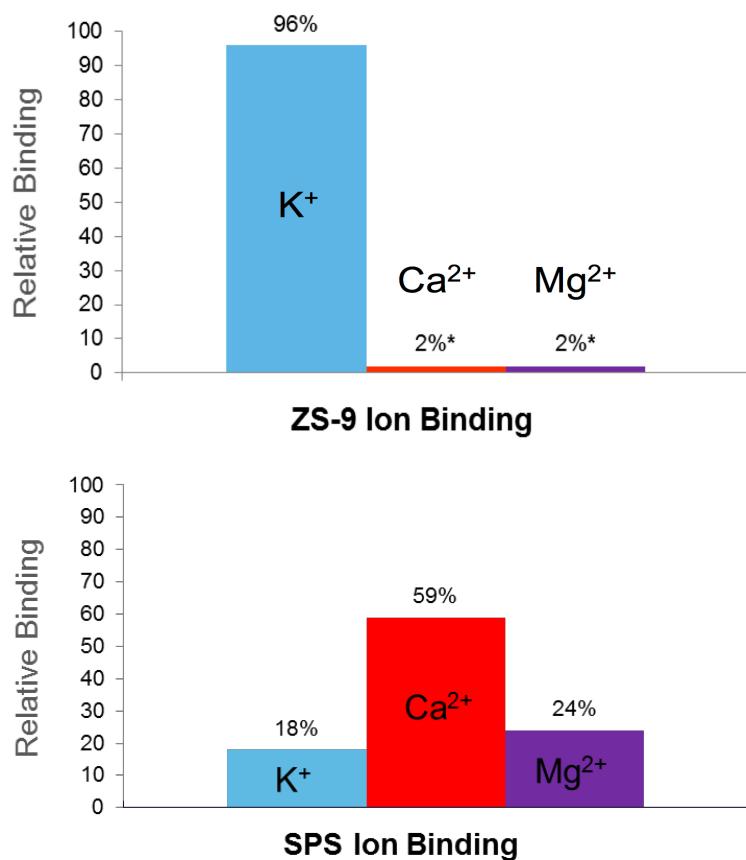


Source: Yang, A. et al., 2014

² Yang, A. et al., 2014. Optimizing the ZS-9 potassium ion trap: Pore size and thermodynamics. *51st European Renal Association and European Dialysis and Transplant Association Congress*, Abstract SP-1.

The oxygen atoms in the crystal structure are arranged to optimally coordinate positively charged ions with a 3 angstrom ionic diameter such as potassium and ammonium. The sized based coordination disfavors smaller and larger ions such as magnesium, calcium, and sodium, thus the compound can trap potassium even in the presence of other positive ions. In contrast, organic polymers like *Kayexalate*/SPS are non-selective and bind potassium only in areas of high potassium concentration like the colon. This inherent difference in selectivity was demonstrated *in-vitro* by comparing the binding of ZS-9 and *Kayexalate*/SPS in the presence of potassium (K^+), calcium (Ca^{2+}), and magnesium (Mg^{2+}) ions at a 1:1:1 ratio. Whereas *Kayexalate*/SPS shows a preference for Ca^{2+} over K^+ or Mg^{2+} , ZS-9 is nearly 100% selective for K^+ , which is depicted in **Figure 2**. We believe this selectivity underlies ZS-9's ability to provide statistically significant benefit in 1 hour and to deliver high potency throughout the GI tract.

Figure 2. Ion Selectivity of ZS-9 Versus *Kayexalate*/SPS



Source: ZS Pharma Reports

ADME and Physical Properties

ZS-9 is an insoluble, odorless, tasteless spherical powder, which thus far, has been formulated as a powder and tablet. The compound does not swell in the presence of water and is effectively eliminated from the body without the need for cathartics to induce diarrhea as is often required with SPS. ZS-9 is thermally stable and essentially insoluble under physiologic conditions. Exposure of the powder form of ZS-9 to simulated gastric and intestinal fluids for an extended period of time resulted in negligible increases in the levels of soluble zirconium (Zr), silicon

(Si), and oxygen (O). These experiments suggest that the amount of Zr released from a 10 g dose of ZS-9 would be less than 0.005% of human daily dietary Zr intake from food and water. **Figure 3** shows the amount of Zr in several sources relative to the amount released from a 10 g dose of ZS-9.^{3,4,5} The figure illustrates that Zr exposure from ZS-9 will not be a significant source of the element for patients. The Company has also conducted *in-vivo* mass balance studies supporting that ZS-9 is excreted in feces and is not systemically absorbed.

Though zirconium exposure from ZS-9 appears to be negligible, zirconium has a long safety history in nephrology applications including hemofiltration, hemodialysis, peritoneal dialysis, and in the design and construction of wearable artificial kidneys.⁴ Notably zirconium containing sorbent columns have been used in over 6,000,000 sessions since the 1970s without safety issues and zirconium containing sorbent columns are currently being developed by the leading dialysis provider Fresenius.⁶ It is important to point out that in sorbent hemodialysis sessions patients with CKD with little or no kidney function have their blood exposed directly to zirconium containing columns. The amount of zirconium directly released into the blood of patients during each session has been quantified to be 0.758 mg, or almost 3,000 times that of a 10 g dose of ZS-9.⁷ More than 40 years of experience with zirconium compounds in biomedical applications and the non-absorbable nature of ZS-9 support the safety and tolerability of ZS-9.

Figure 3. Products Containing Zirconium

Product	Amount	Relative to ZS-9
85 g Antiperspirant Stick	2295 mg	8,196,429x
Soil	300 mg/L	1,071,429x
Human Body Content	300 mg	1,071,429x
Daily Food Content	3.65 mg	13,036x
Zr From 4Hr Sorbent Hemodialysis	0.758 mg	2,707x
Daily Drinking Water Content	0.65 mg	2,321x
Absorption from Antipersperant	0.0046 mg/app.	16x
Sea Water	0.004 mg/L	14x
Soluble from 10 g ZS-9	0.00028 mg	1.0x

Source: H. Schroeder;³ D. Lee,⁴ R. Flarend;⁵ and ZS Pharma Reports

³ Schroeder, H.A. and Balassa, J.J., 1966. Abnormal Trace Metals in Man: Zirconium. *J Chron Dis*, 19(5), pp573-586.

⁴ Lee, D.B. et al., 2010. Zirconium: Biomedical and Nephrological Applications. *ASAIO Journal*, 56(6), pp550-556.

⁵ Flarend, R. et al., 2001. A preliminary study of the dermal absorption of aluminium from antiperspirants using aluminium-26. *Food Chem Toxicol*, 39(2), pp163-168.

⁶ <http://www.renalsolutionsinc.com/history.html>

⁷ Odell RA: Sorbent dialysis, in Nissenson AR, Fine RN, Gentile DE (eds), Clinical Dialysis. Norwalk, CT, Appleton-Century-Crofts, 1990, pp712-719.

Clinical Data

ZS Pharma is advancing ZS-9 through a comprehensive development program with the goal of garnering approval for the extended treatment of hyperkalemia, regardless of the underlying cause. The Company has clear guidance from the FDA and EMA and could receive approval by Q1 2016. The Company has presented positive Phase II data from ZS002 and positive Phase III data from ZS003, including data from the extended treatment phase of the trial. A second Phase III study completed enrollment in July 2014 and a long-term safety study was initiated in June 2014. **Figure 4** below shows the clinical plan and timeline. Note that full ZS005 data is not required for an NDA submission.

Figure 4. Clinical Development Plan for ZS-9

2012				2013				2014				2015				2016			
Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
ZS002 Phase II (n=90)				ZS003 Phase III (n=753)				ZS004 Phase III (n=258)				ZS005 Phase III (estimated 500 patients)				NDA submission		Potential approval	

Source: LifeSci Advisors

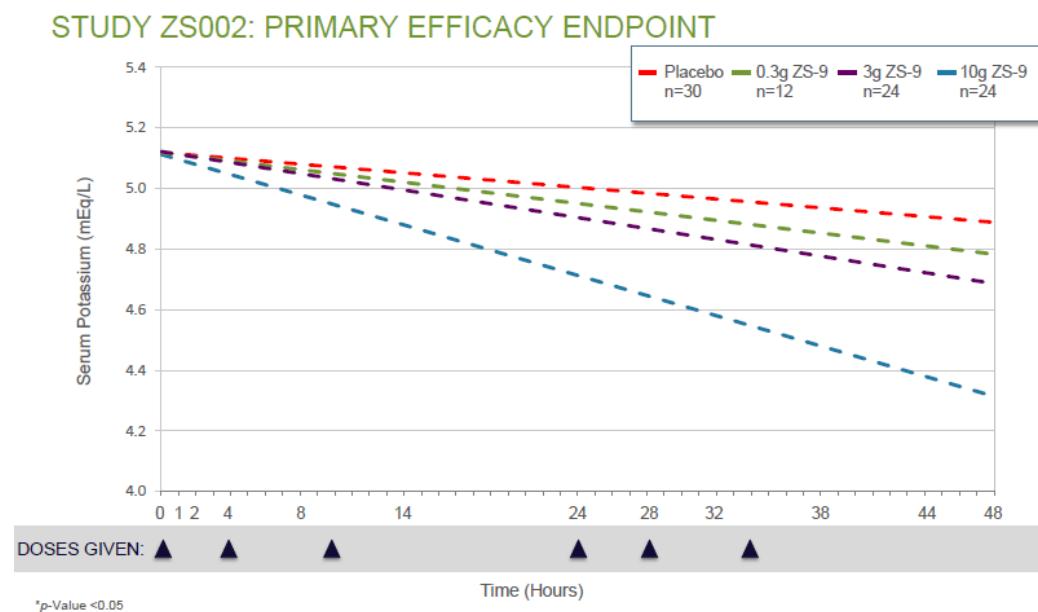
ZS002: Phase II Data Shows Rapid Control of Hyperkalemia. ZS Pharma conducted a Phase II randomized, placebo-controlled, double-blind study that tested three doses of ZS-9 in 90 patients with chronic kidney disease (eGFR 30-60 mL/min) and mild to moderate hyperkalemia (5.0-6.0 mEq/L).⁸ The study was designed to explore ZS-9's ability to rapidly treat hyperkalemia. Patients received 0.3, 3, or 10 grams of ZS-9 or placebo three times daily with meals for 48 hours. Potassium levels were measured at multiple time points during the 48 hour treatment phase as well as once daily during the 5 day follow up period. The primary endpoint of the study was the rate of change in serum potassium over 48 hours.

ZS-9 Shows High Efficacy and Clear Dose Response in ZS002. As shown below in **Figure 5**, there was a clear dose response relationship between ZS-9 and serum potassium levels, and the study met the primary endpoint for the 3 gram ($p=0.048$) and 10 gram ($p<0.0001$) doses of ZS-9. Of particular note, the 10 gram dose produced a dramatic decrease in serum potassium, reducing levels by 0.92 mEq/L in only 38 hours.

⁸ <http://clinicaltrials.gov/ct2/show/NCT01493024>

Figure 5. Effect of ZS-9 Treatment on Serum Potassium Levels over 48 Hours

INTENT-TO-TREAT POPULATION				
Primary Endpoint: Rate of Change of Serum Potassium Over 48 Hours				
	Placebo Pooled	Cohort 1 300mg TID	Cohort 2 3g TID	Cohort 3 10g TID
Primary Endpoint (p-Value)	N/A	0.4203	0.0480	<0.0001
Mean K⁺ Change at 48h mEq/L (14h post last dose)	-0.20	-0.30	-0.35	-0.68
Max K⁺ Change at 38h mEq/L (4h post last dose)	-0.26	-0.39	-0.42	-0.92

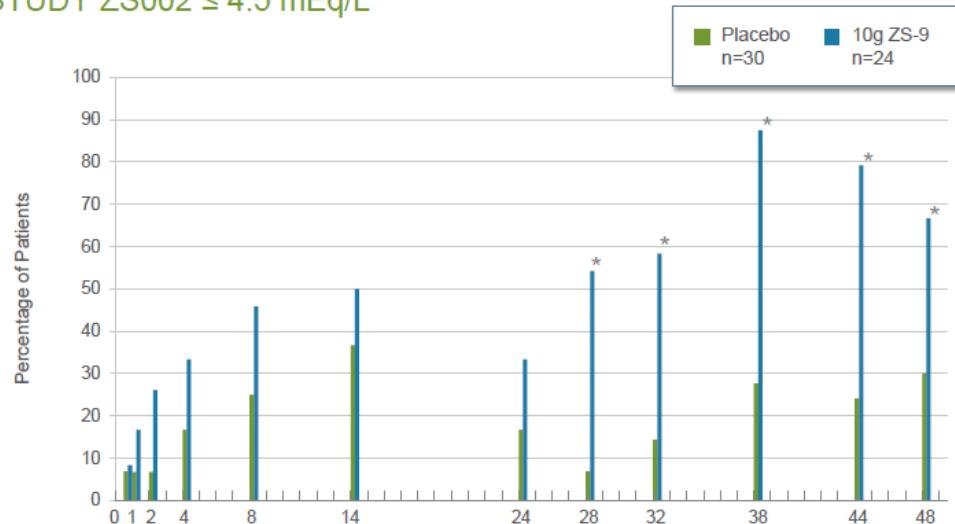


Source: ZS Pharma Reports

Patients receiving the 10 gram dose also experienced high response rates to treatment at 38 hours, where 100% of patients had serum potassium less than 5.1 mEq/L and 90% had serum potassium \leq 4.5 mEq/L. The percentage of patients with serum potassium levels \leq 4.5 mEq/L during the 48 hour treatment period is displayed in **Figure 6**. Furthermore, patients on renin-angiotensin aldosterone (RAAS) inhibitor therapy showed similar responses to those not on RAAS inhibitor therapy. RAAS inhibitors cause serum retention in the kidneys and often lead to hyperkalemia. The data are a good indication that ZS-9 can treat hyperkalemia caused by RAAS inhibitor therapy.

Figure 6. Percentage of Patients with Serum Potassium ≤ 4.5 mEq/L

STUDY ZS002 ≤ 4.5 mEq/L

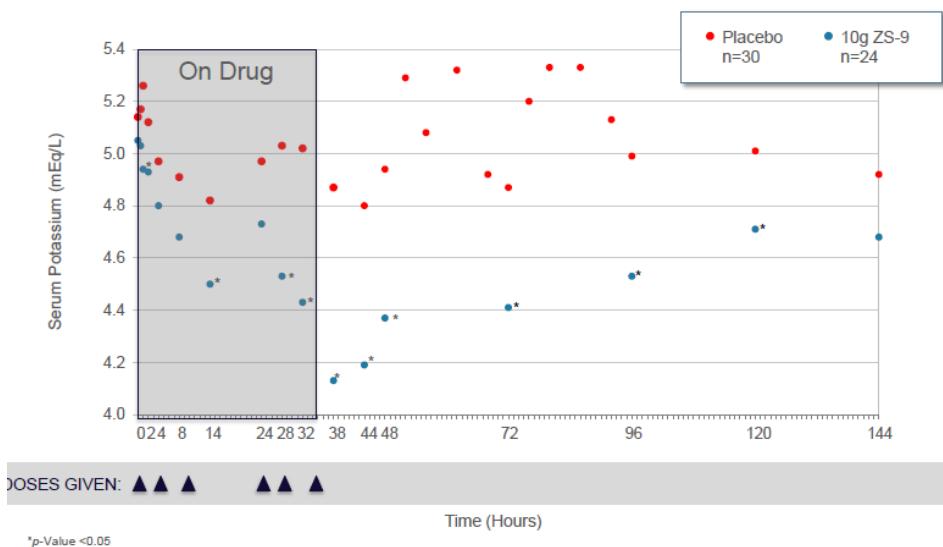


Source: ZS Pharma Reports

Follow-up Period Underscores Need for Chronic Treatment of Hyperkalemia. The follow up period provided some interesting insights for the extended treatment of hyperkalemia. The results are shown in **Figure 7**. Potassium levels rose in patients after ZS-9 therapy was halted, returning to near baseline levels after only days without therapy. This rapid rebound shows that patients with a hyperkalemic episode will rapidly return to an elevated risk state if therapy is not maintained.

Figure 7. Serum Potassium Levels Post-ZS-9 Treatment

STUDY ZS002: MEAN K⁺ OVER 6 DAYS



Source: ZS Pharma Reports

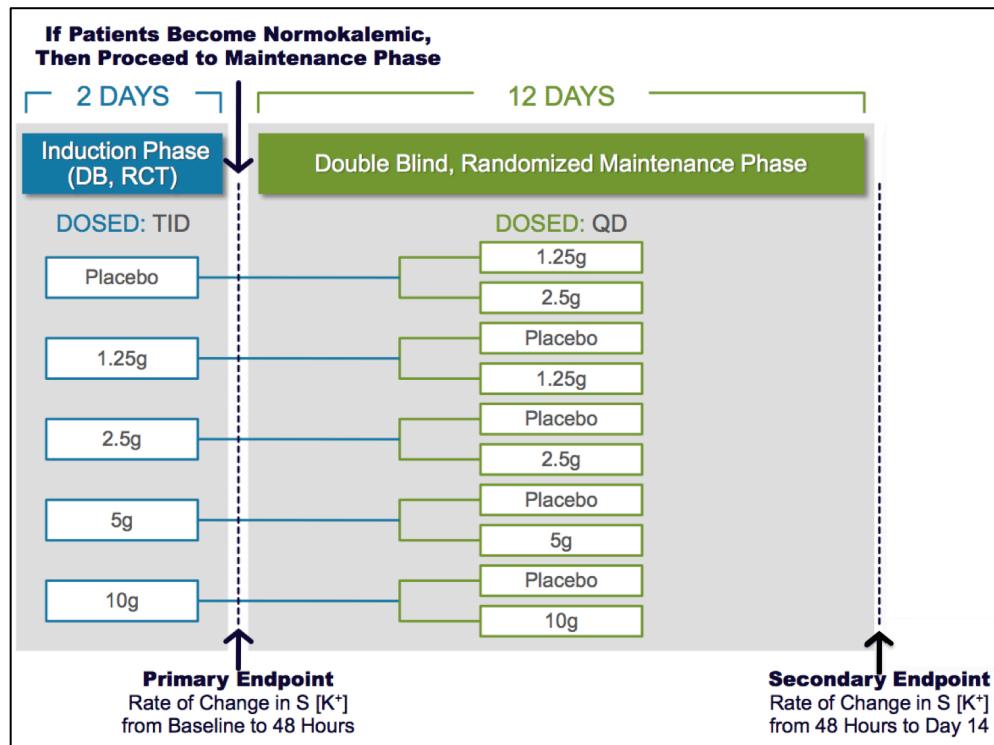
ZS-9 was Well-Tolerated. The adverse event (AE) profile of ZS-9 was favorable, as depicted in **Figure 8**. Transient minimal to mild GI AEs were the most frequent AEs reported. There were no discontinuations, no serious AEs, no clinically significant changes in non-potassium serum electrolytes, and no cases of significant hypokalemia. It is worth noting that the 753 patient, Phase III ZS003 study indicated a safety profile for ZS-9 that was stronger than indicated by the results of this 90 patient trial.

Figure 8. Phase II Adverse Event Profile

No. (%) of patients	Placebo (N=30)	ZS-9 Dose Group (TID)		
		0.3g (N=12)	3g (N=24)	10g (N=24)
Nausea	1 (3)	0 (0)	1 (4)	2 (8)
Vomiting	1 (3)	0 (0)	0 (0)	3 (13)
Urinary tract infection	0 (0)	0 (0)	1 (4)	2 (8)

Source: ZS Pharma Reports

ZS003: Phase III Confirms ZS-9's Potency, Rapid Onset of Action, and Tolerability, and Indicates Potential for Long-term Use. ZS003 was a randomized, double-blind, placebo-controlled, pivotal Phase III clinical trial that enrolled 753 patients with hyperkalemia (potassium levels 5-6.5 mEq/L), and included patients with chronic kidney disease (CKD), heart failure, diabetes, and those on RAAS inhibitor therapy. The study was designed to confirm ZS-9's ability to rapidly treat hyperkalemia (Induction Phase) and also explore the ability of ZS-9 to maintain normokalemia (Extended Treatment Phase). Patients were randomized to receive one of four doses of ZS-9 (1.25, 2.5, 5, or 10 grams) or placebo, administered three times daily for the initial 48 hours (Induction Phase). The primary endpoint was the rate of change in serum potassium from baseline throughout the 48 hour Induction Phase, which was the same primary endpoint used in the ZS-002 study. Patients normalized ($K < 5.0$ mEq/L) in the Induction Phase were then randomized to active drug (1.25, 2.5, 5, or 10 grams) or placebo administered once-daily for 12 days (Extended Treatment Phase). The endpoint for the randomized withdrawal Extended Treatment Phase was the rate of change in serum potassium during the 12-day dosing period. Enrollment was rapid, a clear indicator of the high prevalence of hyperkalemia, and 80% of patients were from the United States. The study design is illustrated in **Figure 9**.

Figure 9. Phase III Trial Design


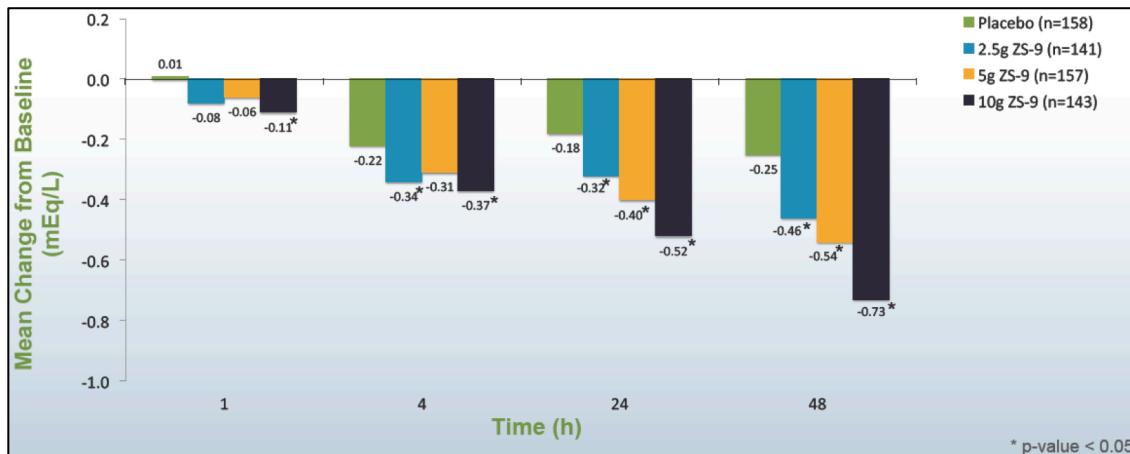
Source: El-Shahawy, M.A. et al., 2014

ZS-9 Rapidly Reduces Potassium and Maintains Normokalemia for 12 Days. ZS-9 showed significant, rapid, and dose-dependent reductions in serum potassium at the 2.5, 5, and 10 gram doses.

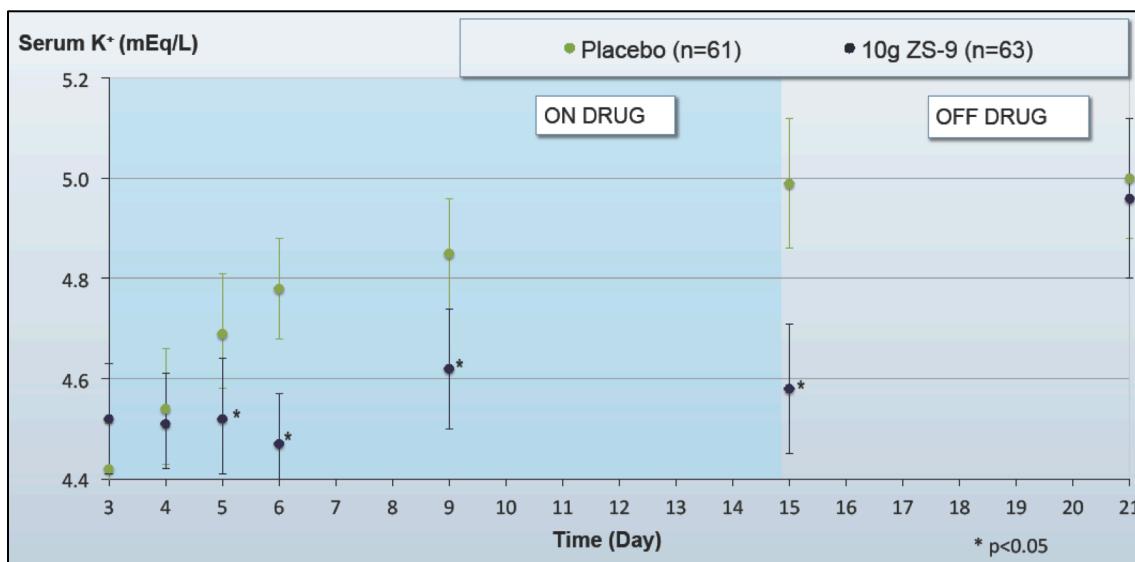
- The trial met the primary efficacy endpoint for the Induction Phase at the 2.5, 5, and 10 gram doses compared with placebo ($p=0.0009$, <0.0001 , and <0.0001 , respectively).
- Mean serum potassium reduction was -0.73 mEq/L at the 10 gram dose at 48 hours ($p<0.0001$), 14 hours after the last dose.
- Patients in the Extended Treatment Phase maintained a statistically and clinically significant reduction in serum potassium compared to placebo ($p=0.0075$ and <0.0001 , respectively).

ZS-9 led to a rapid reduction in serum potassium, with a significant decrease in levels as early as 1 hour post treatment with the 10 gram dose. All doses led to a significant reduction in potassium by 24 hours and the reduction continued until the end of the acute phase at 48 hours. The mean change in serum potassium from baseline is shown for all dose groups in **Figure 10.**⁹ By 48 hours, patients receiving 10 grams of ZS-9 three times daily experienced a potassium reduction of -0.73 mEq/L.

⁹ El-Shahawy, M.A. et al., 2014. Acute-phase efficacy in a Phase 3 multicenter, randomized, double-blind, placebo-controlled trial of ZS-9 for hyperkalemia. *51st European Renal Association and European Dialysis and Transplant Association Congress*, Poster #SP320.

Figure 10. Serum Potassium Reduction in Acute Phase

Source: El-Shahany, M.A. et al., 2014

Patients treated with 5 or 10 grams of ZS-9 in the Extended Treatment Phase maintained normokalemia for 12 days with once daily dosing, whereas serum potassium rebounded to hyperkalemic levels in subjects receiving placebo. **Figure 11** shows serum potassium levels for patients receiving 10 grams of ZS-9 or matched placebo.¹⁰ Six days after patients stopped receiving ZS-9 treatment their serum potassium returned to levels observed in placebo patients.

Figure 11. Serum Potassium Reduction in Extended Treatment Phase

Source: Roger, S.D. et al., 2014

¹⁰ Roger, S.D. et al., 2014. Extended efficacy of ZS-9 once-daily in a Phase 3 multicenter, randomised, double-blind, placebo-controlled trial of patients with hyperkalaemia. *51st European Renal Association and European Dialysis and Transplant Association Congress*, Poster #SP331.

Significant Potassium Reduction Observed in RAAS Inhibitor Population. ZS Pharma presented data at several conferences this spring demonstrating that ZS-9 reduces serum potassium in patients receiving RAAS inhibitors.¹¹ **Figure 12** shows the breakdown of RAAS inhibitor use in patients treated in the Acute and Extended Treatment Phases. The figure displays the percentage of patients receiving each type of inhibitor. Most patients were on an ACE inhibitor or angiotensin II receptor blocker (ARB). A smaller fraction were taking a mineralocorticoid-receptor antagonist (MRA) or a combination of two of the three inhibitors.

Figure 12. Patients Receiving RAAS Inhibitor Therapy in Acute and Extended Treatment Phases

	Acute Phase		Extended Phase	
	Placebo (n=158)	10g ZS-9 (n=143)	Placebo (n=61)	10g ZS-9 (n=63)
ACEi, %	40.5	44.8	42.6	46.0
ARB, %	23.4	23.1	23.0	23.8
MRA, %	7.0	4.2	6.6	3.2
ACEi + ARB, %	2.5	1.4	1.6	1.6
ACEi + MRA, %	3.2	0.7	1.6	0.0
ARB + MRA, %	1.9	2.8	3.3	3.2
ACEi + ARB + MRA, %	0.0	0.0	0.0	0.0

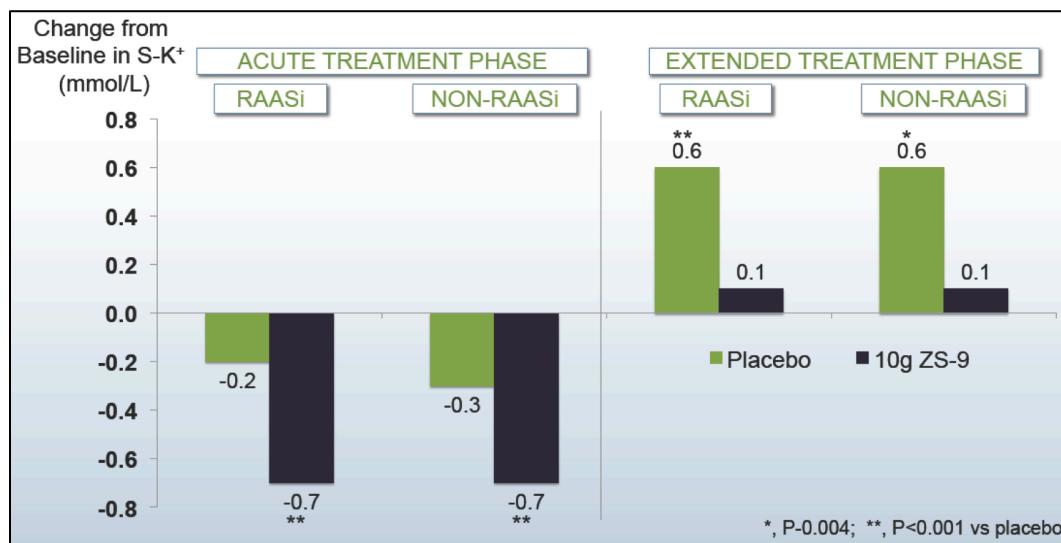
ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blockers; MRA, mineralocorticoid-receptor antagonist

Source: Roger, S.D. et al., 2014

Patients receiving RAAS inhibitors experienced a significant decrease in serum potassium levels in both the Acute and Extended Treatment Phases that was similar to patients not on RAAS inhibitor therapy. The data are shown in **Figure 13**. In the Acute Treatment Phase, the mean decrease in potassium from baseline was a statistically significant -0.7 mmol/L for the 10 gram ZS-9 arm for both subsets of patients ($p<0.001$ versus placebo). In the Extended Treatment Phase, the change in potassium from the end of day 3 to day 15 for the ZS-9 arm was +0.1 mmol/L, indicating that patients maintained normokalemia. In contrast, RAASi patients in the placebo arm experienced a significant +0.6 mmol/L increase in potassium over the same time period ($p<0.001$).

¹¹ Roger, S.D. et al., 2014. Efficacy of ZS-9 in patients receiving RAAS therapy: A subgroup analysis of a Phase 3 multicenter, randomised, double-blind, placebo-controlled trial. *51st European Renal Association-European Dialysis and Transplant Association*. Poster #SP324.

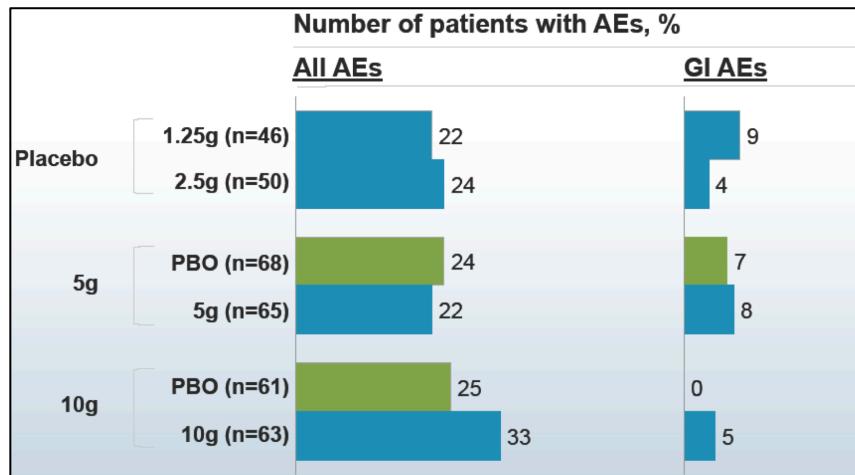
Figure 13. Change in Serum Potassium from Baseline by RAAS Inhibitor Subgroup and Treatment Phase



Source: Roger, S.D. et al., 2014

The Phase III subset data further reinforce ZS-9's ability to significantly reduce serum potassium in patients receiving RAAS inhibitors. The data indicate that ZS-9 may allow patients to remain on RAAS inhibitors and receive the substantial benefits derived from these medications, but avoid developing hyperkalemia and the associated side effects. The benefits of RAAS inhibitors may drive adoption of ZS-9 in a population that typically manages hyperkalemia by reducing RAAS inhibitor dose.

Low Adverse Event Rate, GI Adverse Event Rate Similar to Placebo. One of the key results from the extended portion of the trial is that ZS-9 was well-tolerated over 12 days. Across all doses, the incidence of AEs was similar to placebo in the Induction Phase, as shown in **Figure 14**. Given the high incidence of GI AEs observed with polymer resins like *Kayexalate*, of particular note is the similar gastrointestinal (GI) AE rate in patients receiving ZS-9 and placebo.

Figure 14. Extended Treatment Phase Adverse Event Profile

Source: Roger, S.D. et al., 2014

Extended Treatment Phase Data a Primer for Upcoming 1 Month Maintenance Study (ZS004). ZS Pharma completed enrollment of the Phase III ZS004 trial in July 2014. The trial is intended to support the extended use of ZS-9. The design of ZS004 is similar to ZS003, except that treatment is extended for a total of 6 months, including a double-blind placebo-controlled withdrawal period for 28 days of treatment. ZS004 has a good probability of success considering the similar trial design to ZS003 and the modest change in treatment duration.

ZS005 Will Test Long-Term Safety and Efficacy. In June 2014, ZS Pharma initiated enrollment of ZS005, a multi-dose, open-label safety study designed to show the long-term safety of once daily dosing of ZS-9. The trial will enroll approximately 500 patients who will receive 10 gram of ZS-9 three times daily during the Induction Phase, which occurs over 24 to 72 hours. Patients will then receive 5 gram of ZS-9 once daily for 12 months in the Maintenance Phase. Titration of ZS-9 will occur in this phase if needed to maintain normokalemia. Based on interactions with the FDA and EMA, the Company believes this development program will be sufficient for approval of ZS-9 in both the US, Europe, and additional foreign markets. The filing of an NDA is expected in the first half of 2015.

Chemistry, Manufacturing, and Controls

Cost-Effective Manufacturing and Storage. The chemistry, manufacturing, and controls (CMC) for ZS-9 have been well described by the company. Considerable optimization has resulted in a reliable and robust process that produces ZS-9 in high yield from readily available raw materials. The product is a stable inorganic compound that requires no special handling or temperature control, translating to low cost of goods sold. ZS Pharma plans to manufacture ZS-9 at two wholly owned GMP facilities located in Texas and Colorado. The Company has increased its manufacturing capabilities and expects to be producing at commercial scale by the fourth quarter of 2014. We predict that ZS-9 will be on par with small molecules in terms of gross margins.

Many Product Presentations Possible with ZS-9. ZS-9 is a free flowing white powder that easily suspends and has no odor or taste. It can be formulated as a powder, tablet, capsule, suspension, or sprinkle, making the product convenient for patients.

Intellectual Property & Licensing

ZS Pharma's patent estate covers composition of matter, method of use, and formulation out beyond 2032. The Company received Notices of Allowance in July 2014 for a composition of matter patent (13/371,080) and a patent (14/036,489) that covers methods of treating hyperkalemia. Given the specialized knowhow and equipment required for producing ZS-9 and the non-systemic nature of ZS-9, technical and regulatory barriers may provide an additional layer of protection beyond 2032.

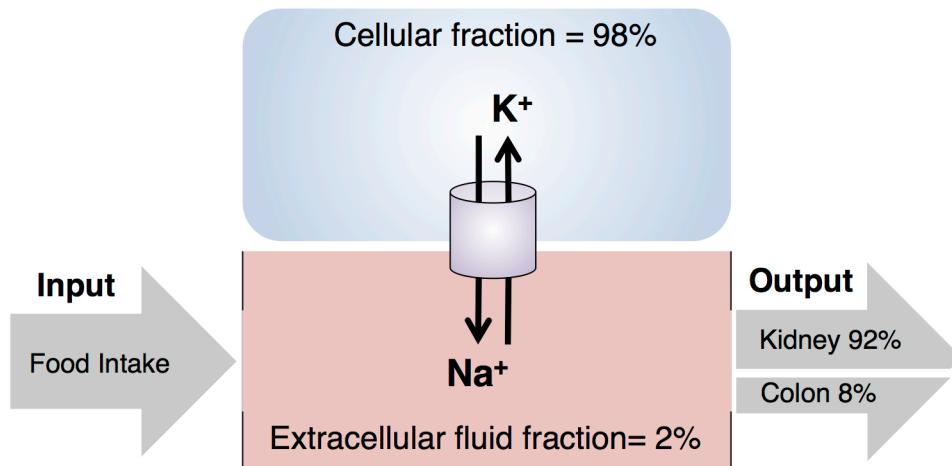
Hyperkalemia Background

Potassium's Role in the Body and Impact on Cardiac Function. Potassium has an important role in normal human physiology, especially with regard to the firing of action potentials in nerve and muscle cells, and is the most abundant intracellular cation. **Figure 15** shows the distribution and flow of potassium in the body. The balance and regulation of potassium in the blood requires an appropriate level of intake through food and the effective elimination via the kidneys and digestive tract. Under non-disease conditions, the amount of potassium intake equals the amount of elimination, and hormones such as aldosterone act in the kidneys to stimulate the removal of excess potassium. Approximately 98% of all potassium is found inside cells versus 2% in the extracellular fluid (ECF), including blood, and that gradient is maintained via well-studied sodium/potassium (Na^+/K^+) pumps.¹² Hormones such as insulin act on Na^+/K^+ pumps to increase the intracellular level of potassium and are an important regulatory mechanism to maintain the intracellular/extracellular balance of these ions.¹³ In fact, administration of insulin with glucose is a short-term method for shifting serum potassium levels by forcing the element inside the cell.

¹² Gouaux, E. et al., 2005. Principles of selective ion transport in channels and pumps. *Science*, 310(5753), pp1461-1465.

¹³ Sweeney, G. et al., 1998. Regulation of the Na^+/K^+ -ATPase by insulin: why and how? *Molecular and Cellular Biochemistry*, 182(1-2), pp121-133.

Figure 15. Distribution and Flow of Potassium in the Body



Source: Adapted from Giebisch, G.H., 2002¹⁴

Role of Potassium in Action Potentials. Potassium and sodium ions drive action potentials in nerve and muscle cells by actively crossing the cell membrane and shifting the membrane potential, which is the difference in electrical potential between the exterior and interior of the cell. Excess serum potassium can disrupt the membrane potential in cardiac cells that regulate ventricular conduction and contraction. In addition to active transport, K⁺ can move passively between the extracellular and intracellular compartments. An overload of passive K⁺ transport, caused by higher levels of blood potassium, depolarizes the membrane in the absence of a stimulus, but is not sufficient to trigger an action potential. Decreased contraction of the cardiac tissue manifests as potentially fatal heart arrhythmias, and is the main risk for patients with hyperkalemia.

Hyperkalemia – Excess Serum Potassium. Hyperkalemia is a disease of excess potassium in the extracellular fluid, including the blood. Normal blood potassium levels are between 3.5-5.0 mEq/L.¹⁵ Figure 16 displays a modified version of the three degrees of hyperkalemia based on the ERC guidelines.

Figure 16. Degree of Hyperkalemia

Degree of Hyperkalemia	Blood Potassium Level (mmol/L)
Mild	5.0-5.5
Moderate	5.5-6.4
Severe	≥6.5

Source: Soar, J. et al., 2010¹⁶

¹⁴ Giebisch, G.H., 2002. A train of research on potassium. *Kidney International*, 62(5), pp1498-1512.

¹⁵ Kratz, A et al., 2004. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Laboratory reference values. *The New England Journal of Medicine* 351 (15): 1548–63.

¹⁶ Soar, J. et al., 2010. European Resuscitation Council Guidelines for Resuscitation 2010 Section 8. Cardiac arrest in special circumstances: Electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. *Resuscitation*, 81, pp1400-1433.

Hyperkalemia is caused by deficiencies in potassium excretion, and most commonly affects patients with kidney diseases such as CKD, since the kidney is the primary mechanism of potassium removal. The use of RAAS inhibitors in HF patients is also a significant driver of hyperkalemia, often leading to the under-treatment (removal of RAAS inhibitor) and improper management of HF due to the risk of hyperkalemia-induced arrhythmias. The connectivity of the potassium distribution system complicates efforts to manage the disease long-term, as patients may have one of the above conditions plus excessive dietary intake, compounding the retention of potassium. ZS-9 is able to remove potassium from the blood regardless of the etiology of the disease, and could offer a one-size-fits-all approach to hyperkalemia management.

Unmet Medical Need

Hyperkalemia is a Life-Threatening Medical Condition. The impact of hyperkalemia on mortality is well documented,^{17,18,19,20} and is a result of potassium's importance in the firing of action potentials in nerve and muscle cells. Cardiac arrhythmias are the leading cause of mortality in hyperkalemia patients, and the condition can develop with few symptoms until cardiac arrhythmias manifest and hospitalization is required. Several studies have independently documented the risk of death or cardiac events associated with hyperkalemia, and represent many different patient populations, including those with previous acute myocardial infarctions,²¹ previously hospitalized veterans,²² intensive care patients,²³ dialysis patients,²⁴ and veterans with heart failure on medication for hypertension.²⁵ The consistency of the findings suggests a strong connection between excess serum potassium and the risk of death.

The morbidity and mortality impact of hyperkalemia is significant. Hyperkalemia is detected in between 1% and 10% of all hospitalized patients. In one study the 1-day mortality rate was up to 17 times higher for admitted patients with serum potassium above 6.0 mEq/L versus those with serum potassium less than 5.5 mEq/L.²⁶ **Figure 17** shows the percentage of patients that died within 1 day of hyperkalemia detection for three ranges of serum potassium levels. Even patients with between 5.5 and 6.0 mEq/L of serum potassium had a 1-day mortality rate 6 times higher than those with less than 5.5 mEq/L.

¹⁷ An, J.N. et al., 2012. Severe hyperkalemia requiring hospitalization: predictors of mortality. *Critical Care*, 16(6), R225.

¹⁸ McMahon, G.M. et al., 2012. Association between hyperkalemia at critical care initiation and mortality. *Intensive Care Med*, 38(11), pp1834-1842.

¹⁹ Dorgaonkar, S. et al., 2010. Serum Potassium and Outcomes in CKD: Insights from the RRI-CKD Cohort Study. *Clin J Am Soc Nephrol*, 5(5), pp762-769.

²⁰ Jain, N. et al., 2012. Predictors of hyperkalemia and death in patients with cardiac and renal disease. *American Journal of Cardiology*, 109(10), pp1510-1513.

²¹ Goyal, A. et al., 2012. Serum potassium levels and mortality in acute myocardial infarction. *JAMA*, 307(2), pp157-164.

²² Einhorn, L.M. et al., 2009. The frequency of hyperkalemia and its significance in chronic kidney disease. *Archives of Internal Medicine*, 169(12), pp1156-1162.

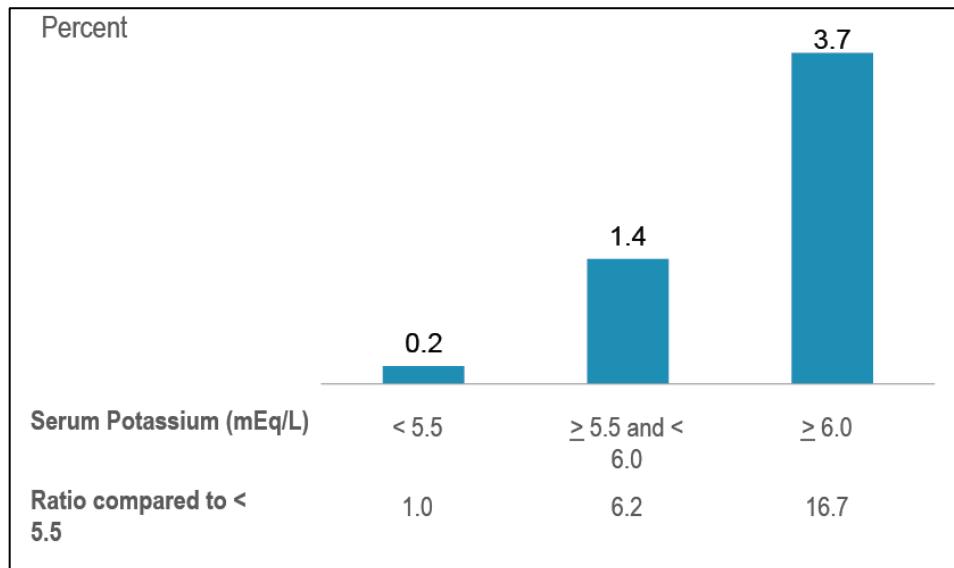
²³ McMahon, G.M. et al., 2012. Association between hyperkalemia at critical care initiation and mortality. *Intensive Care Med*, 38, pp1834-1842.

²⁴ Torlén, K. et al., 2012. Serum Potassium and Cause-Specific Mortality in a Large Peritoneal Dialysis Cohort. *Clin J Am Soc Nephrol*, 7(8), pp1272-1284.

²⁵ Jain, N. et al., 2012. Predictors of hyperkalemia and death in patients with cardiac and renal disease. *American Journal of Cardiology*, 109(10), pp1510-1513.

²⁶ Einhorn, L.M. et al., 2009. The frequency of hyperkalemia and its significance in chronic kidney disease. *Archives of Internal Medicine*, 169(12), pp1156-1162.

Figure 17. Mortality Rate within 1 Day of Hyperkalemia Detection

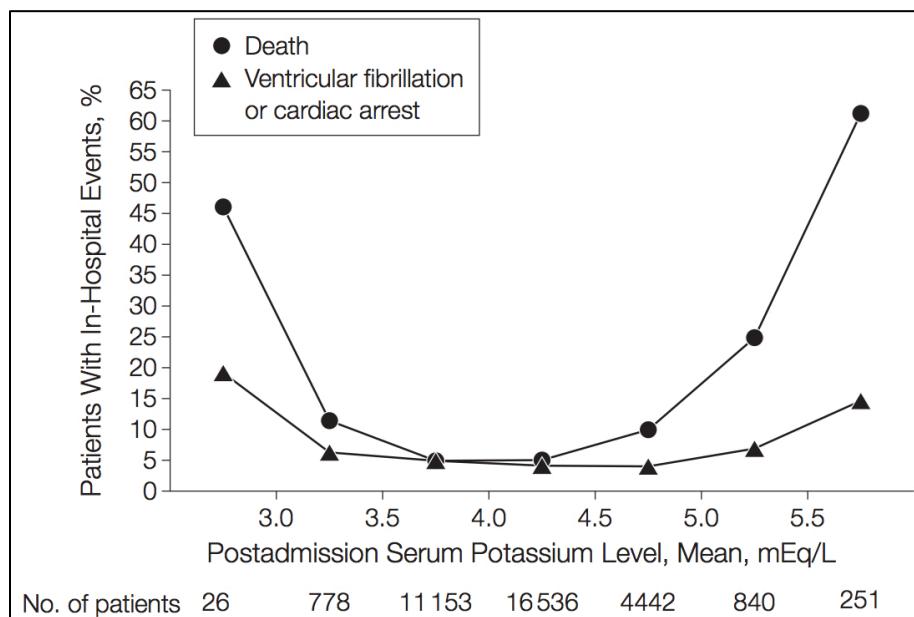


Source: Derived from Einhorn, L.M. et al., 2009

Another recent study published in JAMA showed that sudden death and serious cardiac events increased as serum potassium levels rose above 4.5 mEq/L.²⁷ This retrospective study was the largest of its kind and examined 38,689 patients from 67 hospitals over a 9-year period. The percentage of patients with in-hospital mortality or in-hospital ventricular fibrillation or cardiac arrest was determined for those with several ranges of post-admission serum potassium, and the data are shown in **Figure 18**. Although hyperkalemia patients represented only 3.2% of the total patient population, they accounted for 16% of the total hospital deaths. The results demonstrate that high serum potassium levels are a risk factor for cardiac events and mortality. Therefore, an effective treatment that can maintain normal levels of serum potassium could provide real clinical benefits to these patients and reduce their risk of mortality and cardiac events.

²⁷ Goyal, A. et al., 2012. Serum potassium levels and mortality in acute myocardial infarction. *JAMA*, 307(2), pp157-164.

Figure 18. Rate of In-hospital Mortality of Cardiac Events Relative to Post-Admission Serum Potassium Levels



Source: Goyal, A. et al., 2012

Treating Hyperkalemia Reduces the Risk of Mortality. Studies have confirmed that reducing serum potassium levels in hyperkalemia patients actually reduces the mortality risk, further solidifying the role of excess potassium in the risk of death. One study found that treatment of hyperkalemia with common therapies (except for dialysis) both improved serum potassium levels and resulted in a statistically significant increase in survival.²⁸ Another study, in hospitalized patients receiving critical care, showed that the reduction of serum potassium by ≥ 1 mEq/L 48 hours after hospitalization also decreased the mortality risk.²⁹ These studies suggest that treating hyperkalemia in the acute and chronic settings can have a real impact on patient outcomes by reducing the risk of death.

Cardio-Renal Protective RAAS Inhibitor Therapy is Limited by Hyperkalemia

The renin-angiotensin aldosterone system (RAAS) is important for the regulation of blood pressure and maximum doses of RAAS inhibitors are widely recommended for patients with hypertension, heart failure (HF), chronic kidney disease (CKD), and diabetes. Large outcomes studies have shown that RAAS inhibitors can significantly decrease hospitalization, morbidity, and mortality in these patients. However, inhibition of the RAAS pathway also promotes potassium retention and is a major cause of hyperkalemia. As a consequence, hyperkalemia has led to the suboptimal use of RAAS inhibitors in the treatment of serious diseases such as CKD and HF.

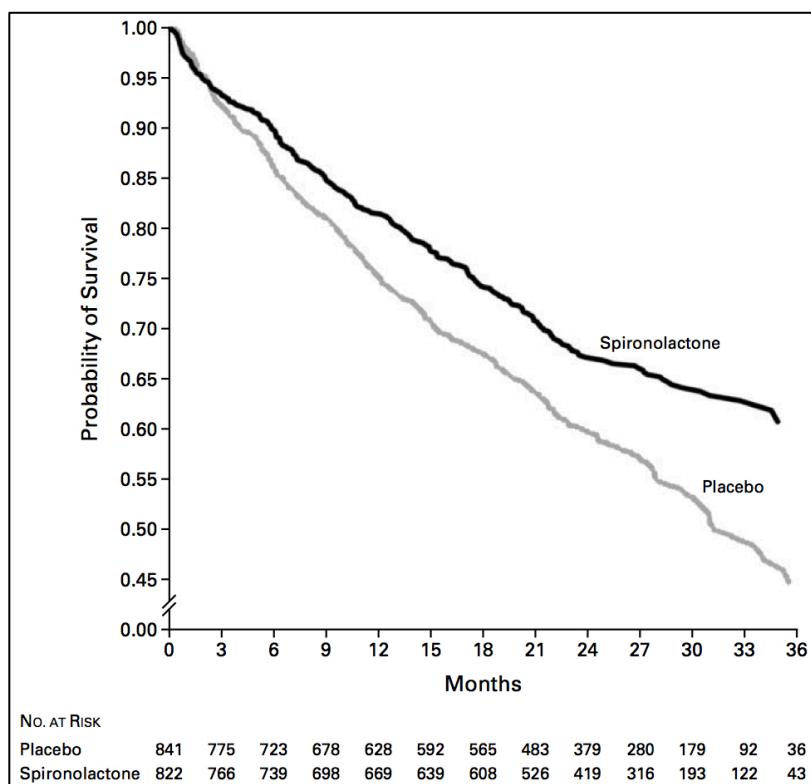
Outcomes Studies Demonstrate the Importance of RAAS Inhibitor Therapy. Large outcomes studies have demonstrated that RAAS inhibitors significantly improve the health of patients. RAAS inhibition reduces mortality

²⁸ An, J.N. et al., 2012. Severe hyperkalemia requiring hospitalization: predictors of mortality. *Critical Care*, 16(6), R225.

²⁹ McMahon, G.M. et al., 2012. Association between hyperkalemia at critical care initiation and mortality. *Intensive Care Med*, 38, pp1834-1842.

and hospitalization rates in heart failure patients by impacting heart function. The inhibitors also reduce all-cause mortality by minimizing damage to secondary organs such as the kidneys and delaying the progression of diabetes. A prominent study (RALES) in heart failure patients showed a significant reduction in death and hospitalization with the aldosterone inhibitor spironolactone, and demonstrated that dose optimization plays a significant role in the efficacy of these drugs. **Figure 19** shows the probability of survival from month 0 to 36 for patients receiving placebo or spironolactone. Patients receiving spironolactone had a much higher probability of survival, especially at later time points after treatment began. Overall the risk of death was 30% lower in the spironolactone group compared to the placebo group.³⁰

Figure 19. Probability of Survival for Placebo and Spironolactone Treated Patients



Source: Pitt, B. et al., 1999

EPHESUS, a 6,632 patient randomized, placebo-controlled study, published in 2003, described the benefit of eplerenone, an aldosterone blocker, on mortality and morbidity in patients with heart failure that have had a previous myocardial infarction.³¹ Another study, the RENAAL trial, demonstrated that the angiotensin receptor

³⁰ Pitt, B. et al., 1999. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. *N Engl J Med*, 341, pp709-717.

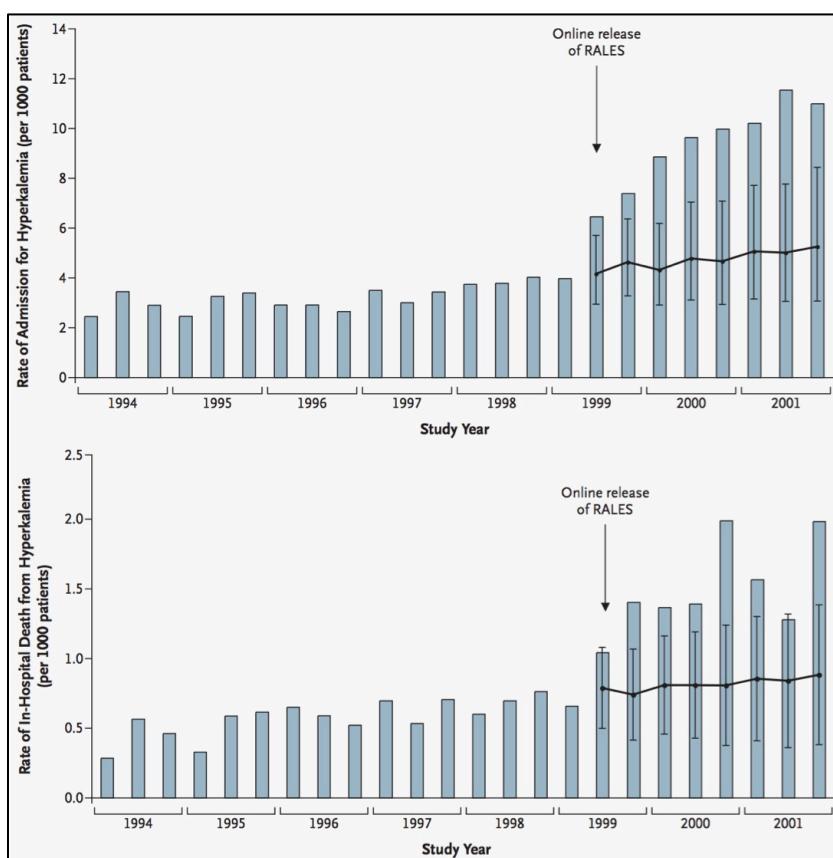
³¹ Pitt, B. et al., 2003. Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction. *N Engl J Med*, 348, pp1309-1321.

blocker losartan delayed progression of CKD to end-stage renal disease and reduced hospitalization in type 2 diabetics.³² This trial specifically highlights the benefits of RAAS inhibition on non-heart conditions.

Hyperkalemia, Mortality, and RAAS Inhibitor Therapy. As a result of these compelling outcomes studies, RAAS therapy is guideline recommended in millions of patients making the class the 3rd most commonly prescribed medication in the US. However, RAAS inhibitors impact aldosterone, a hormone involved in potassium secretion, leading to hyperkalemia.

Both the rate of admission for hyperkalemia and the rate of in-hospital death from hyperkalemia increased following the publication of RALES as shown in **Figure 20**. The rate of hospital admission due to hyperkalemia increased dramatically from a rate of 2.4 per 1000 patients prior to RALES to approximately 11 per 1000 in the two years following RALES publication ($p<0.001$). Furthermore, the rate of in-hospital death from hyperkalemia increased from approximately 0.3 per 1000 patients to 2 per 1000 patients after RALES ($p<0.001$). These data reflect increased use of spironolactone and are not surprising given the effect of RAAS inhibitors on potassium retention and the association of hyperkalemia with mortality discussed above.

Figure 20. Rate of Hospital Admission and Death from Hyperkalemia Before and After RALES

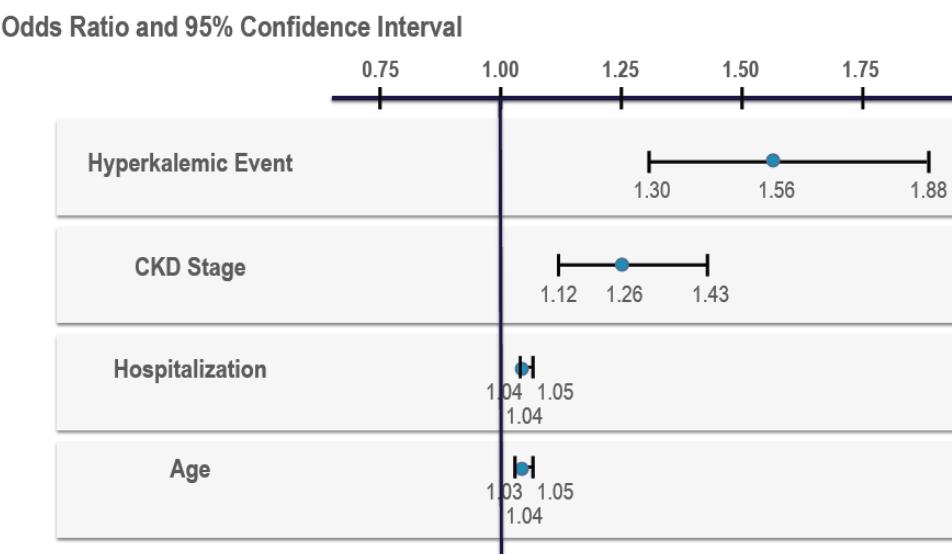


Source: Juurlink, D.N. et al., 2004

³² Brenner B.M. et al., 2001. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *The New England Journal of Medicine*, 345, pp861–869.

A 2012 study published in the *American Journal of Cardiology* in 2012 found that hyperkalemia is the top predictor of all-cause mortality in cardiovascular patients with CKD on anti-hypertensive drugs.³³ The results of the study are displayed in **Figure 21**, and show that hyperkalemia is a stronger predictor of all-cause mortality than CKD stage, hospitalization, or age.

Figure 21. Predictors of All-cause Mortality in Cardiovascular Disease Patients with CKD Receiving Antihypertensive Drugs



Source: Jain, N. et al., 2012

A study published at the end of August 2014 in *The New England Journal of Medicine* showed a high rate of hyperkalemia in patients treated with Novartis's experimental angiotensin receptor-neprilysin inhibitor LCZ696.³⁴ Patients were treated with Merck's ACE inhibitor *Vasotec* (enalapril) or LCZ696 for a median of 27 months, and the trial was stopped early due a strong effect of LCZ696 on reducing death and hospitalization due to HF. LCZ696 reduced the risk of hospitalization for HF by 21% compared to enalapril ($p < 0.001$). If approved by the FDA, LCZ696 could be a leading treatment for patients with HF. However, similar to other agents, LCZ696 led to high rates of hyperkalemia. 16.1% of patients receiving LCZ696 had levels of serum potassium greater than 5.5 mEq/L, compared to 17.3% of patients receiving enalapril. Despite improvements in efficacy, innovative treatments such as LCZ696 still cause hyperkalemia similar to existing therapies. This data highlights the unmet medical need for treatments such as ZS-9 that may allow patients to tolerate these life-saving medications.

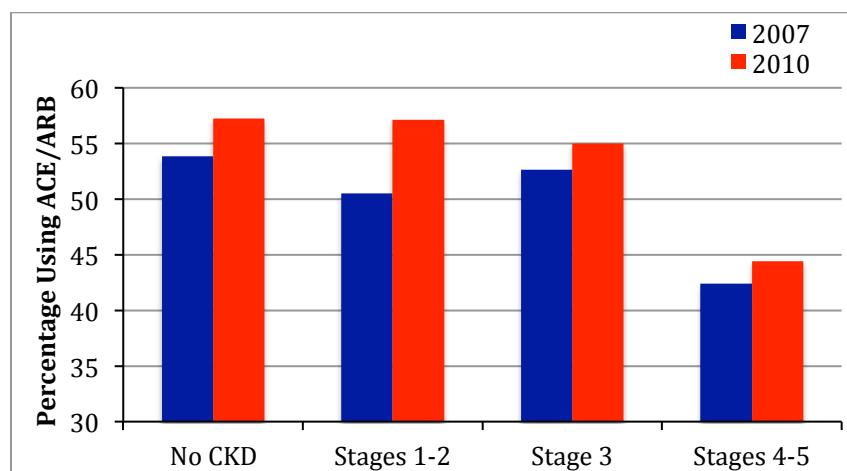
Benefits of RAAS Inhibitors are Not Realized Due to Hyperkalemia. Due to the risk of hyperkalemia, it is not surprising that a large percentage of patients are either not treated with RAAS inhibitor therapy, or are undertreated,

³³ Jain, N. et al., 2012. Predictors of hyperkalemia and death in patients with cardiac and renal disease. *American Journal of Cardiology*, 109(10), pp1510-1513.

³⁴ McMurray, J.J. et al., 2014. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *The New England Journal of Medicine*, Epub ahead of print.

despite clear guideline recommendations and proven patient benefit.³⁵ There is evidence that the majority of heart failure patients are on suboptimal RAAS inhibitor doses, and that up to 15% of heart failure patients are not on RAAS inhibitor treatment at all.^{36,37,38,39,40} In CKD patients with diabetes, over 70% are not treated or treated below targeted dose.⁴¹ The 2012 US Renal Data Survey shows that RAAS inhibitor usage in the Medicare population declines as CKD stage progresses, and suggests this decline is likely due to the impact of hyperkalemia.⁴² **Figure 22** shows the percentage of patients on angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) for 2007 and 2010. The fraction of patients with stage 4 or 5 CKD who are taking ACE inhibitors or ARBs is approximately 10% lower than patients in earlier stages of the disease. A well-tolerated and effective potassium-reducing agent would allow patients to avoid the hyperkalemia associated with RAAS therapy while receiving the full benefit of these medications, including improved mortality and slowed progression to end stage renal disease.

Figure 22. RAAS Inhibitor Use in Patients with Cardiovascular Disease



Source: USRDS 2012 Annual Data Report – ACE/ARB Utilization in CHF by CKD stage

³⁵ Komajda, M. et al., 2003. The EuroHeart Failure Survey programme – a survey on the quality of care among patients with heart failure in Europe. *European Heart Journal*, 24, pp464-474.

³⁶ Lenzen, M.J. et al., 2005. Under-utilization of evidence-based drug treatment in patients with heart failure is only partially explained by dissimilarity to patients enrolled in landmark trial: a report from the Euro Heart Survey on Heart Failure. *European Heart Journal*, 26, pp2706-2713.

³⁷ Echermann, M. et al., 2000. Determinants of angiotensin-converting enzyme inhibitor prescription in severe heart failure with left ventricular systolic dysfunction: The EPICAL study. *American Heart Journal*, 139(4), pp624-631.

³⁸ Peters-Klimm, F. et al., 2012. Physician and patients predictors of evidence-based prescribing in heart failure: a multilevel study. *PLoS One*, 7(2), e31082.

³⁹ Davie, A.P. and McMurray, J.J., 1999. ACE inhibitors and heart failure in hospital: any difference between cardiologists and general physicians. *Postgrad Med J*, 75, pp219-221.

⁴⁰ Bungard, T.J. et al., 2001. Underutilisation of ACE inhibitors in patients with congestive heart failure. *Drugs*, 61(14), pp2021-2033.

⁴¹ Thompson Reuters US RAAS Dosing Study.

⁴² USRDS 2012 Annual Data Report - ACE/ARB Utilization in CHF by CKD stage.

Existing Clinical Guidelines Support Hyperkalemia Treatment

Treatment guidelines are already in place to address the risk of hyperkalemia and its limiting effect on the optimal use of RAAS inhibitors. Guidelines published by the American Heart Association and the American Association of Family Physicians recommend that physicians address hyperkalemia, regardless of underlying cause, if serum potassium exceeds 5.0 mEq/L. In addition, treatment guidelines, including those published by the leading kidney (KDOQI), heart (AHA), and diabetes (ADA) associations, widely recommend the highest dose of RAAS inhibitors to delay progression of kidney disease and decrease morbidity and mortality in heart failure patients. At the same time, these guidelines also recognize that RAAS inhibitors contribute to hyperkalemia, and recommend reduction or elimination of RAAS inhibitor therapy if serum potassium exceeds 5.0 mEq/L. The presence of these guidelines will support the introduction of a new agent to control high potassium to both physicians and payers.

Current Treatments for Hyperkalemia are Ineffective. In the hospital setting, intravenous drugs exist that can stabilize the heart and temporarily reduce serum potassium for up to 4 hours by shifting potassium into the cells. However, no treatment is available to effectively and safely remove excess potassium and maintain normal levels of serum potassium. 1) SPS/*Kayexalate* is the current standard of care treatment for potassium reduction, but its safety and efficacy have never been proven in randomized trials. SPS is poorly tolerated by patients and causes a high incidence of GI side effects (nausea, vomiting, constipation, diarrhea), which leads to poor compliance and renders the drug unsuitable for chronic use. In addition, in 2009 the FDA issued a warning for colonic necrosis that sparked a debate in the medical community on whether SPS/*Kayexalate* should ever be used.⁴³ 2) Low potassium diets are widely prescribed, but enforcing compliance is difficult and, as the underlying disease biology progresses, they lose effectiveness. 3) For patients on RAAS inhibitors, limiting or removing RAAS medications decreases potassium, but puts patient at a higher risk of mortality and/or more rapid disease progression due to uncontrolled hypertension. Given the widely recognized limitations of existing therapies, we believe that there is a significant market for a well-tolerated, effective treatment for hyperkalemia.

US Hyperkalemia Market

Addressable Patient Population. Individuals with CKD and heart failure are the major populations at risk for chronic hyperkalemia due to poor renal function and/or need for treatment with renin-angiotensin aldosterone system (RAAS) inhibitors. Together, CKD and heart failure patients represent over 30 million lives in the US and are expected to grow to nearly 50 million lives by 2022.

CKD Patients and Hyperkalemia. As CKD stage progresses, the risk of hyperkalemia increases. There are approximately 18 million patients in the US with advanced CKD stage 3 or 4,⁴⁴ and approximately 60% of these late stage patients are seeing a nephrologist or cardiologist for treatment.⁴⁵ Based on a large dataset from the VA, about 20% of CKD stage 3 patients and 40% of CKD stage 4 patients have hyperkalemia with serum potassium above 5.5

⁴³ Stapleton, F.B., 2010. Is Kayexalate Effective for Hyperkalemia, and Is It Safe? *NEJM Journal Watch*.

⁴⁴ Coresh, J. et al., 2007. Prevalence of chronic kidney disease in the United States. *JAMA*, 298(17), pp2038-2047.

⁴⁵ USRDS 2013 Annual Data Report. Volume 1, Chapter 2, Table H.

mEq/L.⁴⁶ Extrapolating from these data points results in an estimate of approximately 2.4 million late stage CKD patients with hyperkalemia.

This estimate is generally consistent with ‘bottom up’ patient load estimates from primary market research. For example, BioTrends reports that an average nephrologist treats an average of 288 hyperkalemic patients per year within their practice.⁴⁷ This study did not include hyperkalemia patients treated only by cardiologists.

The most likely patients to be treated for chronic hyperkalemia are those with serum potassium above 5.5 mEq/L and/or those who have a co-morbidity for which RAAS inhibitor therapy is strongly recommended, such as heart failure, diabetes, or uncontrolled hypertension. Roughly 50-60% of CKD patients have been prescribed a RAAS agent within the 12 months following their CKD diagnosis.⁴⁸

Between the large number of late stage CKD treated by a nephrologist or cardiologist with serum potassium above 5.5 mEq/L and the substantial portion of CKD patients with co-morbidities indicated for treatment with RAAS inhibitor therapy, we believe the addressable patient population for chronic hyperkalemia treatment within CKD exceeds 1 million patients.

Heart Failure Patients and Hyperkalemia. Congestive heart failure patients, especially those taking RAAS inhibitors, are another large group that is at risk of developing life-threatening levels of serum potassium. The decreased heart output and corresponding low blood flow through the kidneys, coupled with inhibition of aldosterone, can lead to chronic hyperkalemia. Approximately 5.7 million individuals in the US have congestive heart failure.⁴⁹ Over half of these patients are taking at least one RAAS inhibitor, including angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), or aldosterone receptor antagonists (AAs).^{50,51,52,53,54} Of the 2.8 million heart failure patients currently on RAAS inhibitor therapy, studies show that two-thirds, or nearly 2 million, are taking a suboptimal dose.^{55,56,57} Based on the literature, we estimate about half of these patients are on a

⁴⁶ Einhorn, L.M. et al., 2009. The frequency of hyperkalemia and its significance in chronic kidney disease. *Archives of Internal Medicine*, 169(12), pp1156-1162.

⁴⁷ BioTrends Treatment Trends: Hyperkalemia, March 2011

⁴⁸ USRDS 2013 Annual Data Report. Volume 1, Figure 5.13.

⁴⁹ Roger, V.L. et al., 2012. Executive summary: heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*, 125(1), pp188-197.

⁵⁰ Sadjadi, S.A. et al., 2009. A comparative study of the prevalence of hyperkalemia with the use of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers. *Therapeutics and Clinical Risk Management*, 5, pp547-552.

⁵¹ Setoguchi, S. et al., 2010. Temporal Trends in Adherence to Cardiovascular Medications in Elderly Patients After Hospitalization for Heart Failure. *Clinical Pharmacology & Therapeutics*, 88(4), pp548-554.

⁵² Masoudi, F.A. et al., 2005. The Complexity and Cost of Drug Regimens of Older Patients Hospitalized With Heart Failure in the United States. *Arch Intern Med*, 165, pp2069-2076.

⁵³ DiMartino, L.D. et al., 2010. Use of Guideline-Recommended Therapies for Heart Failure in the Medicare Population. *Clin. Cardiol*, 33(7), pp400-405.

⁵⁴ Lachaine, J. et al., 2011. Use, tolerability and compliance of spironolactone in the treatment of heart failure. *BMC Clinical Pharmacology*, 11(4).

⁵⁵ Echemann, M. et al., 2000. Determinants of angiotensin-converting enzyme inhibitor prescription in severe heart failure with left ventricular systolic dysfunction: The EPICAL study. *American Heart Journal*, 139(4), pp624-631.

⁵⁶ Komajda, M. et al., 2003. The EuroHeart Failure Survey programme – a survey on the quality of care among patients with heart failure in Europe. *European Heart Journal*, 24, pp464-474.

suboptimal dose due specifically to hyperkalemia.⁵⁸ After addressing the potential overlap with the CKD patient population addressed above, this represents about 400,000 to 500,000 heart failure patients that would benefit from a potassium control agent to enable therapeutic doses of cardio-protective RAAS inhibitor therapy.

Conservatively, the addressable patient population within the US for a chronic hyperkalemia therapy exceeds 1.4 million patients. We also believe that with the advent of a safe and tolerable potassium control agent, physicians will treat more aggressively with RAAS inhibitors and the addressable patient population is likely to increase.

Acute Hyperkalemia. Acute hyperkalemia is often treated in the hospital. According to the Centers for Disease Control and Prevention (CDC), there were 35.1 million hospital discharges in 2010. Hyperkalemia is detected in between 1 and 10% of all hospitalized patients. In the hospital setting, intravenous drugs exist that can stabilize the heart and temporarily reduce serum potassium for up to 4 hours, but shortly thereafter patients develop hyperkalemia once again because the potassium remains in the body. Thus, *Kayexelate* is often given after the temporizing medications to eliminate potassium. Based on 2011 IMS US data, 200 million grams of *Kayexelate* are sold in the non-retail setting annually. Based on a 15 gram dose, we estimate over 13 million doses of *Kayexelate* are given in the hospital setting.⁵⁹

Given ZS-9's clinical profile, we expect it to be used as an alternative to *Kayexelate* in the hospital setting. ZS-9 may face some headwinds based on the cost relative to generic SPS in the hospital setting, however, if ZS-9 replaces merely a third of the *Kayexelate* used in the hospital, we believe sales in this setting could reach \$100 million annually.

Pricing and Market Penetration

We expect ZS-9 to be priced similarly to other oral specialty products in the CKD market, such as *Sensipar*, a calcimimetic, and *Renagel*, a phosphate binding agent. We expect pricing around \$600 per month to be acceptable to payers based on the strong clinical imperative, the existing treatment guidelines, lack of safe and tolerable alternatives, and the compelling pharmaco-economic value story related to enabling RAAS inhibition. Given the targeted specialty market and unmet need, we expect ZS-9 to be available on payer formularies without restriction. Considering patient compliance and physician prescribing patterns, we estimate that adherence to extended therapy would conservatively be around 50%, generating per patient revenue of approximately \$3,600 annually.

Based on our analysis, we believe the addressable market for hyperkalemia could be as large as \$4 billion in the US. We believe ZS-9's safety and tolerability profile will allow ZS Pharma to build a new market for the extended treatment of hyperkalemia and capture a substantial portion of sales, even in light of the competition addressed later in the report. Thus, our total estimate for the market potential of ZS-9 in hyperkalemia is approximately \$1.2 - \$1.3 billion at peak. In addition, we expect hospital sales to generate an additional \$100 million.

⁵⁷ Lenzen, M.J. et al., 2005. Under-utilization of evidence-based drug treatment in patients with heart failure is only partially explained by dissimilarity to patients enrolled in landmark trial: a report from the Euro Heart Survey on Heart Failure. *European Heart Journal*, 26, pp2706-2713.

⁵⁸ Ahuja, T.S. et al., 2000. Predictors of the Development of Hyperkalemia in Patients Using Angiotensin-Converting Enzyme Inhibitors. *Am J Nephrol*, 20, pp268-272.

⁵⁹ IMS US *Kayexelate* Script Data (non-retail). March 2011.

Given the concentration of hyperkalemia within nephrology and cardiology, we believe ZS-9 can reach this market with a 100-150 person specialty sales force targeting 7,000 nephrologists and 15,000 non-interventional cardiologists within heart failure focused practices.

We Believe our Estimate is Conservative. The ability to treat patients with chronic hyperkalemia for extended periods will be a paradigm-shift for nephrologists and cardiologists. With the advent of a safe and tolerable potassium control agent, nephrologists and cardiologists will have a tool to more aggressively treat hyperkalemia and increase the use of RAAS inhibitor therapy in at-risk patients, thus increasing the market size for ZS-9. Because we assume that ZS Pharma will have a specialty sales force focused on nephrology and cardiology, our analysis does not include additional patient populations often addressed by internists or other specialties -- such as those with diabetes, hypertension patients on RAAS inhibitors without underlying CHF or CKD, and those taking other hyperkalemia-inducing medications. Over time, it is reasonable to expect some use of ZS-9 in these additional markets.

Competitive Landscape

Hyperkalemia is most often treated by reducing potassium intake and removing RAAS inhibitor therapy where possible. *Kayexalate* is not used to treat chronic hyperkalemia due to the poor tolerability and safety profile coupled with unproven efficacy. ZS Pharma does face competition from Relypsa (RLYP), which has completed Phase III hyperkalemia studies with its drug patiromer. Relypsa plans to file the patiromer NDA in the fourth quarter of 2014, slightly earlier than the expected filing for ZS-9.

***Kayexalate* (Sodium Polystyrene Sulfonate or SPS)**

A Polymer Resin with Unproven Efficacy. *Kayexalate* (sodium polystyrene sulfonate or SPS) is the only FDA approved treatment for hyperkalemia. It was approved by the FDA in 1958, before efficacy studies were required, thus its efficacy has not been clearly established in clinical trials. GI tolerability of SPS is very poor. It does not pass through the digestive system quickly and can lead to fecal impaction, so its use is typically supplemented with sorbitol or other laxatives. There is an active debate on the efficacy of *Kayexalate*, as well as human potassium excretion data, shown below, that suggest sorbitol alone is as efficacious as *Kayexalate* with sorbitol for treating hyperkalemia.^{60,61,62} **Figure 23** shows the total stool water and soluble potassium output in patients receiving laxative alone and laxative plus *Kayexalate*. The potassium output was similar in patients receiving sorbitol alone versus sorbitol plus *Kayexalate*. Although *Kayexalate* did increase potassium output when in combination with another laxative, phenolphthalein, this combination is no longer available due to concern regarding phenolphthalein's toxicity.

⁶⁰ Emmett, M. et al., 1995. Effect of three laxatives and a cation exchange resin on fecal sodium and potassium excretion. *Gastroenterology*, 108, pp752-760.

⁶¹ Watson, M. et al., 2010. Damned If You Do, Damned If you Don't: Potassium Binding Resins in Hyperkalemia. *Clin J Am Soc Nephrol*, 5, 1723-1726.

⁶² Kessler, C. et al., 2011. The use of sodium polystyrene sulfonate in the inpatient management of hyperkalemia. *J Hosp Med*, 6(3), pp136-140.

Figure 23. Fecal Excretion of Potassium at 12 hours in Patients Receiving Laxative +/- *Kayexalate*

	Stool Water (g/12h)	Total K⁺ output soluble (mEq/12h)
Sorbitol 60 gm	714	26
Sorbitol 60 g plus resin 30 gm	657	30
Sorbitol 120 g	1503	32
Sorbitol 120 g + resin 30 gm	1523	29
Phenolphthalein	1265	37
Phenolphthalein + resin	1500	49*

p<0.01, estimated 0.7 K⁺ mEq/gm resin

Source: Emmett, M. et al., 1995

SPS/*Kayexalate* Safety Concerns. In addition to poor tolerability, SPS suffers from poor selectivity and an FDA warning regarding increased risk of colonic necrosis. Because the negatively charged oxygen atoms on polymer resins have no inherent selectivity, polymers like SPS non-specifically bind cations, including potassium, sodium, calcium, and magnesium. This non-specific binding leads to electrolyte disturbances that can complicate their use, particularly in the chronic setting. In addition, organic polymers swell in aqueous physiologic conditions, which may be the source of GI discomforts observed with SPS. The FDA issued a warning in January 2011 due to risks of fatal colonic necrosis. Several reports in the literature support the FDA decision.^{63,64,65} Although a rare occurrence, the complication was fatal in the majority of patients. As a result of these issues, *Kayexalate* is used almost exclusively for the short-term management of hyperkalemia.

Patiromer

A Non-Absorbable Organic Potassium Binding Polymer. Patiromer is a tasteless, odorless powder of uniform spheres, which binds and removes potassium from the GI tract, particularly the colon. Like ZS-9, patiromer is insoluble and non-absorbable and does not require co-administration with a laxative. It is a cross-linked organic polymer constructed from methyl-2-fluoroprop-2-enoate, diethenylbenzene, and octa-1,7-diene. Based on *in-vitro* studies, patiromer has approximately twice the total potassium binding capacity of SPS. Its *in-vitro* selectivity profile

⁶³ Gerstmann, B.B. et al., 1992. Intestinal necrosis associated with postoperative orally administered sodium polystyrene sulfonate in sorbitol. *Am J Kidney Dis*, 20(2), pp159-161.

⁶⁴ Rashid, A. and Hamilton, S.R., 1997. Necrosis of the gastrointestinal tract in uremic patients as a result of sodium polystyrene sulfonate (*Kayexalate*) in sorbitol: an underrecognized condition. *Am J Surg Pathol*, 21(1), pp60-69.

⁶⁵ McGowan, C.E. et al., 2009. Intestinal necrosis due to sodium polystyrene sulfonate (*Kayexalate*) in sorbitol. *South Med J*, 102(5), pp493-497.

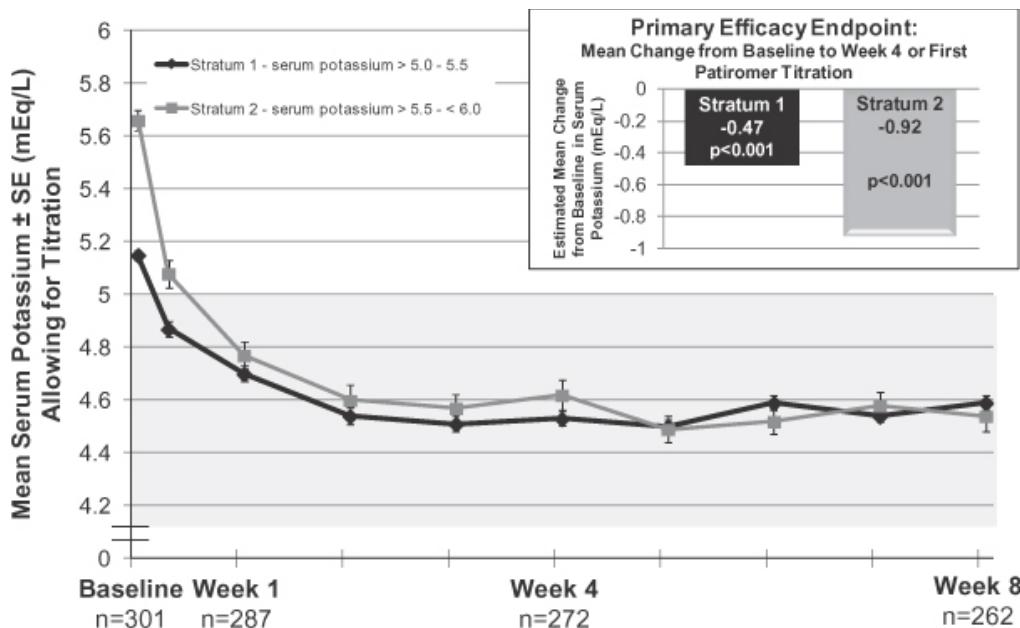
has not been reported, however hypomagnesemia occurred in 24% of patients taking 15g of patiromer BID in a trial with heart failure patients.⁶⁶

Phase I Rapid Onset-of-action Study. Relypsa recently completed a Phase I, open-label, single-arm trial to assess patiromer's ability to rapidly decrease serum potassium. The trial included a 3 day run-in period to control for diet, followed by a 48 hour treatment period with 8.4 grams of patiromer twice daily. Patients were followed for an additional 7 day safety period. A total of 25 patients were enrolled with baseline serum potassium of 5.5 to 6.5 mEq/L. Patiromer led to a significant decrease in serum potassium by 7 hours post-treatment that was maintained to 48 hours ($p<0.001$ at 48 hours). The time to onset is an important contrast with ZS-9. In ZS Pharma's Phase III trial (ZS003), 10 grams of ZS-9 led to a significant reduction in serum potassium by 1 hour post-treatment. Additionally, larger drops in serum potassium are often observed in patients with higher baseline levels. Relypsa's study enrolled patients with baseline serum potassium between 5.5 and 6.5 mEq/L. The final mean potassium levels remained above 5.0 mEq/L. This is in contrast to patients in the ZS003 trial who achieved serum potassium levels near 4.5 mEq/L from a baseline of 5.3 mEq/L. ZS Pharma expects to release additional data regarding time to onset at upcoming medical meetings.

RLY5016-205 Phase IIb Design. Relypsa conducted an uncontrolled, open-label, randomized, dose-ranging, Phase IIb trial that enrolled 306 hyperkalemic patients with chronic kidney disease or type 2 diabetes, all who were also currently receiving RAAS inhibitor treatment. Trial participants were assigned to one of two strata. Strata 1 included patients with baseline serum potassium of 5.1 to 5.5 mEq/L, and strata 2 included patients with baseline serum potassium of 5.6 to 6.0 mEq/L. Patients were randomized to one of three starting doses of patiromer depending on their stratum, and the amount of patiromer was titrated based on individual serum potassium levels. The primary endpoint was the mean change in serum potassium from baseline to week 4 or time to first dose titration. Patients had the option of remaining in the study for an additional 44 weeks to monitor the long-term effects of patiromer on safety and efficacy.

RLY5016-205 Phase IIb Results. The trial met the primary endpoint. After 4 weeks of treatment, patients in strata 1 reduced serum potassium levels by -0.47 mEq/L ($p<0.001$), while those in strata 2 reduced serum potassium by -0.92 mEq/L ($p<0.001$). **Figure 24** shows the serum potassium levels for strata 1 and strata 2 at baseline and across 8 weeks of treatment. The maximum reduction in serum potassium occurred by week 2 or 3 and was maintained through the remaining 5 to 6 weeks of treatment.

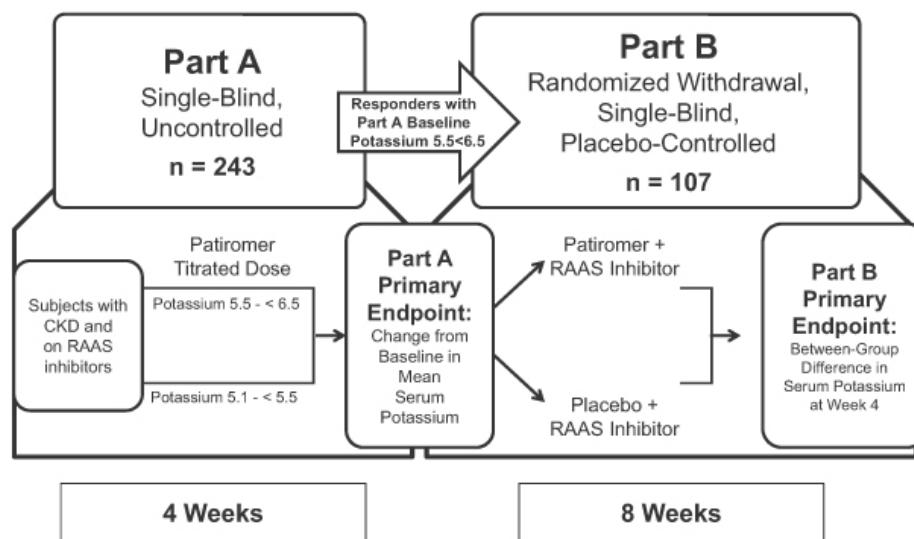
⁶⁶ Pitt, B. et al., 2011. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *European Heart Journal*, 32, pp820-828.

Figure 24. Primary Endpoint Data for Phase IIb Trial with Patiromer

Source: Relypsa 2013 10-K

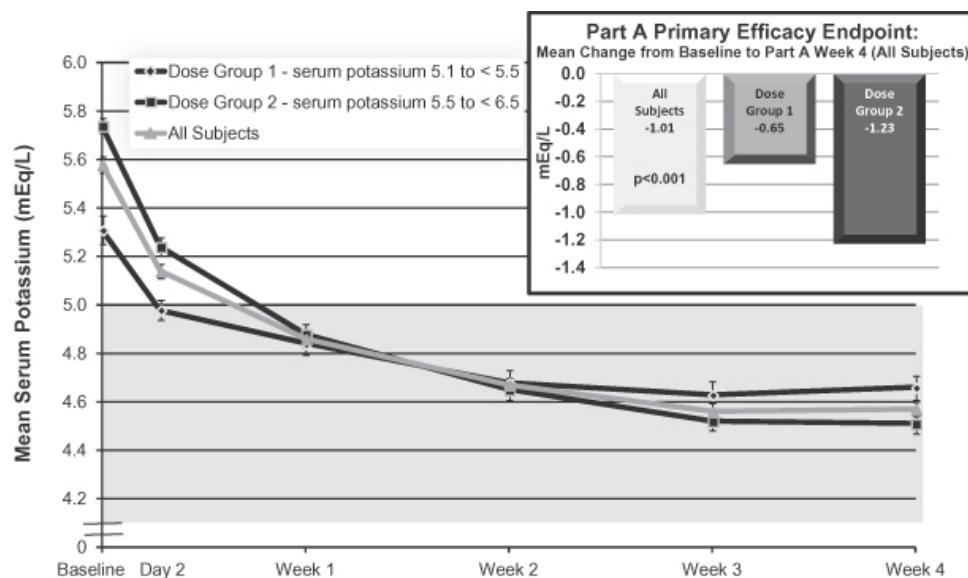
Relypsa's 2013 10-K states that since there was not a clear dose-dependent response to patiromer, the starting doses selected for the Phase III program were 10 grams/day for subjects having a serum potassium level at baseline in the range of 5.1 to 5.5 mEq/L and 20 grams/day for patients having a serum potassium level at baseline above 5.5 mEq/L. With these starting doses, the number of titrations was acceptable with most titrations occurring in the first two weeks.

Phase IIb Long-Term Results. Approximately 64% of subjects completed one year of treatment. The mean serum potassium levels in both strata remained with the target range (3.8 to 5.0 mEq/L) during the 44-weeks of long-term treatment. At the end of the trial, 85.5% of the patients in strata 1 and 89.8% of patients in strata 2 were within the target range.

RLY5016-301 Phase III Trial. Relypsa's Phase III trial was a single-blind, two-part trial testing patiromer in patients with hyperkalemia (5-6.5 mEq/L) and CKD (eGFR 15-60) who were taking an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or an aldosterone antagonist. Part A was a 4-week, single arm, single-blind, patiromer treatment phase and Part B was an 8-week, parallel group, single-blind, placebo-controlled, randomized withdrawal phase. Subjects were enrolled into Part A and were placed in Dose Group 1 if their screening serum potassium was equal to 5.1 to <5.5 mEq/L (starting dose 10 grams/day), or in Dose Group 2 if their screening serum potassium was 5.5 to <6.5 mEq/L (starting dose 20 grams/day). All subjects were titrated to an individual patiromer dose based on their serum potassium levels in order to achieve serum potassium in the range of 3.8 to <5.1 mEq/L. Subjects with a Part A baseline serum potassium level greater than or equal to 5.5 mEq/L and who were defined as responders at the end of Part A were eligible for randomization into Part B. **Figure 25** illustrates the trial design.

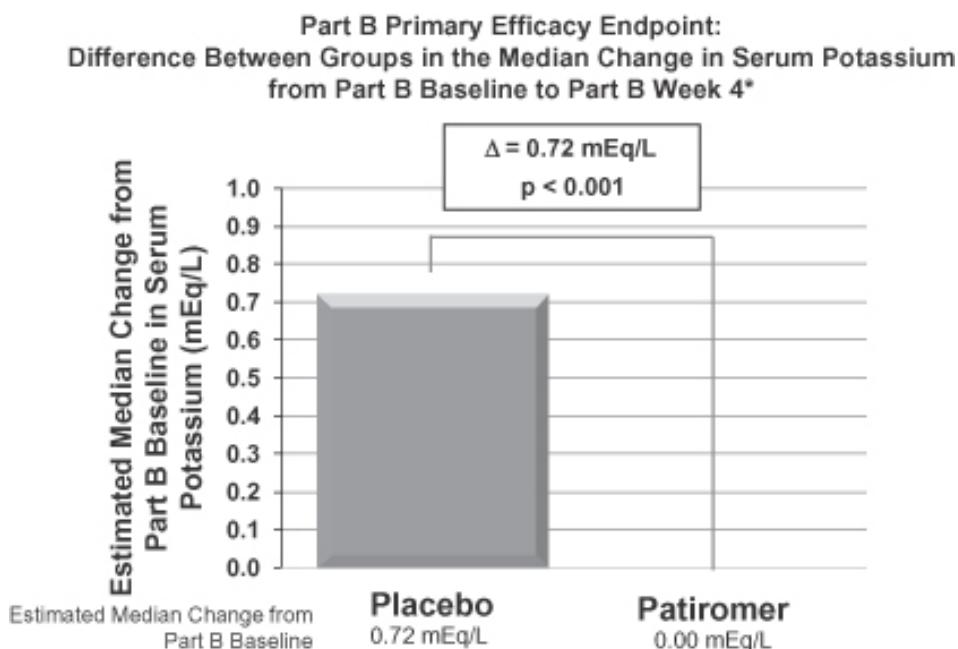
Figure 25. Phase III Trial Design

Source: Relypsa 2013 10-K

Part A Results. Part A enrolled 243 patients. The primary endpoint for Part A was the change in serum potassium from baseline to week 4. The trial met the primary endpoint and showed a statistically significant reduction in serum potassium of -0.65 mEq/L from baseline to week 4 for Group 1 and a reduction in serum potassium of -1.23 mEq/L in Group 2. Across both groups, 76% of subjects reached the normal serum potassium range at week 4. **Figure 26** shows the serum potassium levels for Dose Group 1 and Dose Group 2 at baseline and across 4 weeks of treatment.

Figure 26. Primary Endpoint Data for Phase III Trial with Patiromer

Source: Relypsa 2013 10-K

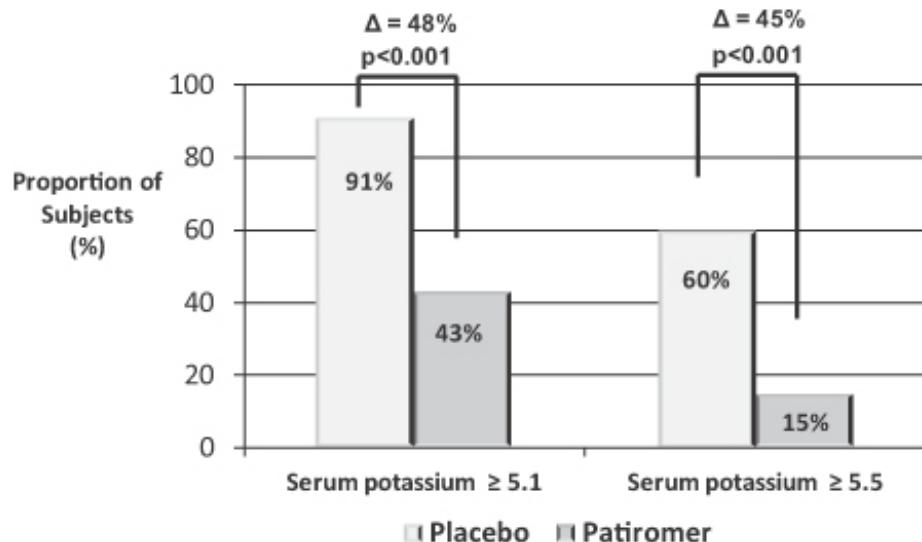
Part B Results. Subjects with a baseline serum potassium level greater than or equal to 5.5 mEq/L at Part A enrollment and whose serum potassium level was controlled at week 4 of Part A were entered into Part B. Part B enrolled 107 patients that were randomized to placebo or patiromer. The primary endpoint for the Part B trial was the difference between the patiromer and placebo groups in the change in serum potassium levels from the start of the Part B period to week 4. Changes were measured at time point before week 4 if alterations to patiromer or RAAS inhibitor therapy were required to control rising serum potassium levels. As shown in the graph below, Part B of the trial met this primary endpoint, with the median change in serum potassium between placebo and patiromer group of 0.72 mEq/L ($p < 0.001$). **Figure 27** highlights the difference between the placebo and patiromer arms. Note that the placebo group experienced an increase in serum potassium versus baseline whereas the patiromer group maintained control of serum potassium levels. Patients were allowed to titrate dose throughout the study.

Figure 27. Primary Efficacy Endpoint for Part B of Phase III Trial



Source: Relypsa 2013 10-K

Deviations from normokalemia were also measured during Part B, and the results are depicted in **Figure 28**. 43% of patiromer subjects had a serum potassium > 5.1 mEq/L at any time during Part B and 15% had serum potassium ≥ 5.5 mEq/L. That is compared to 91% of placebo patients with serum potassium of > 5.1 mEq/L and 60% with serum potassium of ≥ 5.5 mEq/L. The difference between placebo and patiromer was statistically significant for both serum potassium cutoffs.

Figure 28. Proportion of Patients with Recurrent Hyperkalemia During Part B

Source: Relypsa 2013 10-K

Patiromer Safety and Tolerability

GI adverse events potentially related to patiromer have primarily been mild-to-moderate GI symptoms in approximately 20% of subjects, the most common of which were constipation or diarrhea in approximately 5-10% of subjects. Across studies, hypokalemia occurred in 3-6% of patiromer subjects, reductions in mean serum magnesium levels were seen within the first two weeks of treatment of patiromer, and increases in serum fluoride were noted. **Figure 29** highlights the AEs observed in Part A of the Phase III clinical trial.

Figure 29. Adverse Events From Part A in ≥2% of Patients

Total, N=243	AEs, number (%)	Severe AEs, number (%)
Subjects reporting ≥1 AE	107 (44%)	1 (<1%)
Constipation	25 (10%)	0
Diarrhea	8 (3%)	0
Hypomagnesaemia	8 (3%)	0
Nausea	8 (3%)	0
Anemia	6 (2%)	0
Left ventricular hypertrophy	6 (2%)	0
Renal failure chronic	6 (2%)	1 (<1%)
Dyslipidemia	4 (2%)	0
Flatulence	4 (2%)	0
Decreased glomerular filtration rate	4 (2%)	0
Hyperglycemia	4 (2%)	0

Source: Relypsa Reports

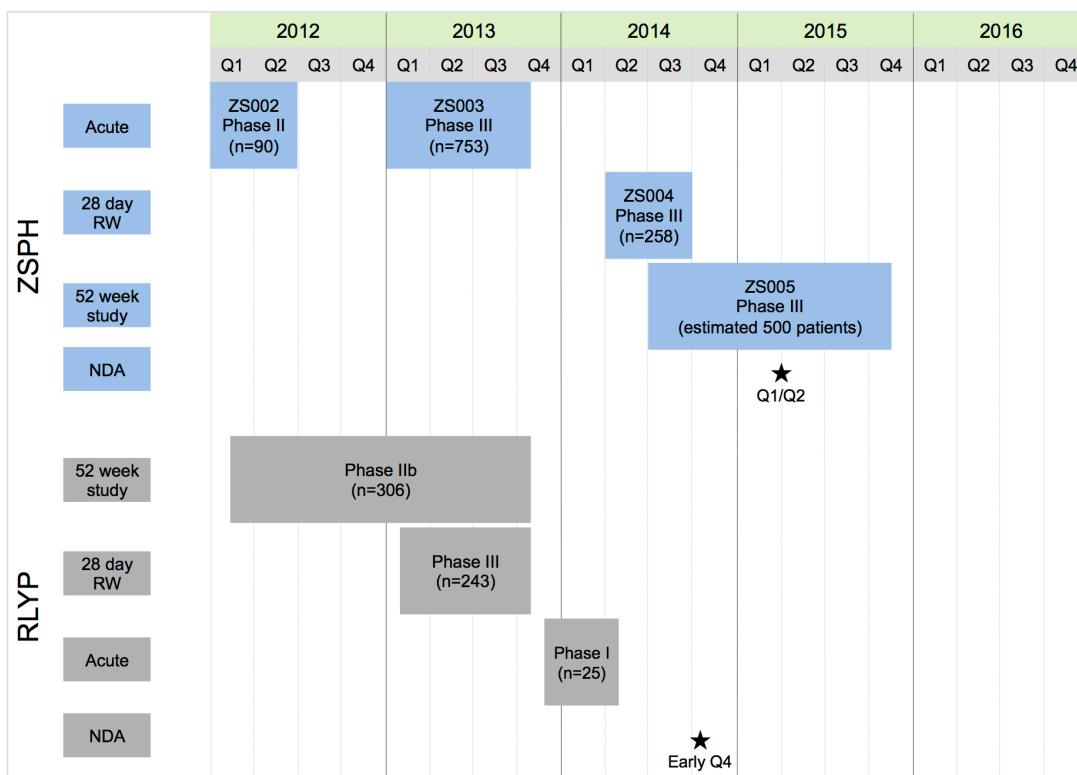
Patiromer Storage and Handling

Currently, patiromer requires cold chain logistics and product handling. Relypsa is testing the stability of patiromer with a combination of cold chain storage and 3-6 months of room temperature stability, and the results of these experiments should be available by the NDA filing.⁶⁷

Comparison of ZS-9 and Patiromer Development Timelines

As illustrated in **Figure 30**, ZS Pharma is on track to file an NDA for ZS-9 by H1 of 2015, while Relypsa is planning its submission in early Q4 of 2014. Both submissions will include similar pivotal datasets including: 1) an acute 48 hour study, double-blind, placebo-controlled in the case of ZS Pharma and open label, single arm in the case of Relypsa, 2) a 28 day placebo-controlled, randomized withdrawal study, single blind with an one month extension for Relypsa and double blind with a 5 month extension for ZS Pharma, and 3) an open label 52 week study. We see a similar timeline between Relypsa and ZS Pharma, and expect product launches to occur within 3-6 months if both products receive FDA approval.

Figure 30. ZS-9 Timeline Versus Patiromer



Source: Relypsa 2013 10-K and ZS Pharma Reports

⁶⁷ Relypsa S-1 filing.

ZS Pharma Management Team

Robert Alexander, Ph.D.

Chairman & CEO

Robert joined ZS Pharma as Executive Chairman in March of 2013. Prior to ZS Pharma, Robert was a Director at Alta Partners, a Venture Capital firm located in San Francisco. In addition, he acted as Executive Chairman and interim CEO of SARcode Biosciences. During his time at Alta, he led investments in SARcode Biosciences (acquired by Shire), Sonexa Therapeutics, Allakos, Lumena Pharmaceuticals, and ZS Pharma.

Prior to Alta, Robert was a Principal in MPM Capital's BioEquities fund where he sourced opportunities and led due diligence efforts for both public and private investments. Robert joined MPM from Genentech where he worked in the Business Development group. At Genentech, his responsibilities included sourcing and screening product opportunities based on scientific merit and strategic fit, leading diligence teams and negotiating terms and definitive agreements.

Prior to joining Genentech, Robert was a post-doctoral fellow at Stanford University in the department of Pathology. He holds a Ph.D. in Immunology from the University of North Carolina and a Bachelor of Arts degree in Zoology from Miami University of Ohio.

Alvaro Guillem, Ph.D.

President

Al co-founded ZS Pharma in 2008. Al is a veteran of the pharmaceutical industry with over thirty years of leadership experience in bringing new therapies to market at both well-established and start-up companies. Prior to ZS Pharma, he held senior positions at Genzyme/Bone Care, Wyeth, Boeringher Ingelheim, as well as start-up companies such as Medeva Americas and Adams Respiratory Therapeutics. Most recently, Al held the role of Vice President of Quality and Scientific Affairs at Ash Access Technology, which developed a catheter lock for patients with ESRD on dialysis.

Al holds a B.S. in Chemistry from Mary Washington University and a Ph.D. in Chemistry from Virginia Commonwealth University.

D. Jeffrey Keyser, RPh, J.D., MPA, Ph.D.

Chief Operating Officer

Jeff co-founded ZS Pharma in 2008 and has over thirty years of experience within the pharmaceutical industry. Prior to joining ZS Pharma, Jeff served as the Chief Compliance Officer and Vice President of Regulatory Affairs at Encysive Pharmaceuticals. In addition, he served as Vice President of Development and Regulatory Affairs at Adams Respiratory Therapeutics and held senior management positions at Medeva Americas, Marion Merrell Dow, Marion Laboratories and Abbott Laboratories.

Jeff has experience in regulatory, medical, clinical and product development and has directed efforts to develop, prepare and secure approvals of numerous INDs and NDAs/MMAAs in the US, Canada, Australia and Europe.

Jeff received his B.S. in Pharmacy and his Doctor of Jurisprudence from Creighton University. He holds a Masters in Public Affairs and Administration from the University of Missouri at Kansas City and a Ph.D. in Economics from the University of Texas at Dallas.

Todd A. Creech, MBA*Chief Financial Officer*

Todd joined ZS Pharma in August 2013. Todd was previously CFO and Vice-President of Business Development at Sarcode Biosciences, where he led all financing, legal, accounting and corporate development activities. Shire Pharmaceuticals acquired Sarcode in April 2013. Prior to Sarcode, Todd was CFO of Sirion Therapeutics, an ophthalmic pharmaceutical company. During his tenure, he raised \$100 million in debt and equity financing to support the development of six late-stage clinical programs, 2 NDA approvals and led the sale of Sirion's drug assets to Alcon and Bausch and Lomb.

Todd worked with NovaQuest, the investment group within Quintiles, Inc, where he structured, placed and managed capital investments into U.S. emerging biotech and specialty pharmaceutical companies. Prior to his work with NovaQuest, he co-founded Centice, an optical sensor spin out from Duke University in 2003. In addition, Todd has an additional 10 years of experience consulting to biotech and high-tech companies while at SRI International and Andersen Consulting. Todd holds bachelor's degrees in Finance and Accounting from Miami (Ohio) University and an MBA from Duke University.

Henrik Sandvad Rasmussen, M.D., Ph.D.*Chief Medical Officer and Chief Scientific Officer*

Henrik joined ZS Pharma in 2012 as Chief Medical Officer. Prior to ZS Pharma, Henrik was the President and CEO of Rasmussen Biotech and Pharma Consulting from 2009-2012. Henrik has held the positions of Corporate Vice President, Head of Clinical Development and Medical and Regulatory Affairs at Novo Nordisk and senior management roles, including Chief Medical Officer for Nabi Biopharmaceuticals and Genvec. He was the Senior Vice President for Clinical Research and Regulatory Affairs at British Biotech and Global Study Director, cardiovascular drug development at Pfizer Central Research.

Henrik has led numerous global development programs and regulatory filings worldwide including INDs, CTAs, NDAs, sNDAs, BLA and MMA filings. He has over 150 published peer-reviewed papers in therapeutic areas including nephrology, cardiology, and diabetes.

Henrik received his M.D. and Ph.D. from University of Copenhagen, Denmark and is trained in internal medicine and cardiology.

Cynthia Smith, MS, MBA*Chief Commercial Officer*

Cynthia joined ZS Pharma in June 2013 as Chief Commercial Officer. Prior to joining ZS Pharma, Cynthia was Vice President, Market Access & Commercial Development at Affymax Inc., a biotechnology company focused on the development and commercialization of novel renal therapies, including a new anemia drug for chronic kidney disease patients.

Prior to Affymax, Cynthia was Executive Director of Healthcare System and Medicare Strategy at Merck. At Merck, Cynthia held various leadership positions in managed markets, corporate strategy, public policy and external affairs, including global crisis management for the Vioxx recall. Before joining the pharmaceutical industry, she served in the White House Office of Management and Budget (OMB) under the Clinton Administration.

Cynthia earned an M.B.A. from the Wharton School, University of Pennsylvania, an M.S. in public policy from the Eagleton Institute, Rutgers University, and a B.A. from the University of North Carolina, Chapel Hill.

Adam L. Tomasi, Ph.D.

Senior Vice President, Corporate Development

Adam joined ZS Pharma as VP of Corporate Development in August of 2013. Previously, Adam was a Principal at Alta Partners, a venture capital firm located in San Francisco, where he invested in multiple private and public companies, including Chemgenex (sold to Cephalon), Excaliard (sold to Pfizer), Lumena Pharmaceuticals (sold to Shire), ZS Pharma (ZSPH), Achaogen (AKAO), Repros (RPRX), Allakos and Immune Design.

Prior to joining Alta, Adam was in the Harvard-MIT Biomedical Enterprise Program where he completed fellowships in venture capital at MPM Capital and as an equity analyst at Lehman Brothers. Originally trained as an organic chemist, Adam spent seven years in early stage drug discovery with Gilead Sciences and Cytokinetics, where he played a key role in the creation of cardiovascular drug CK-1827452, which was licensed to Amgen.

Adam holds a bachelor's degree in chemistry from UC Berkeley, an M.B.A. from the MIT Sloan School of Management, and a Ph.D. in chemistry from U.C. Irvine, where he was a Fellow of the American Chemical Society and UC Regents and a post-doctoral student at The Scripps Research Institute.

Mark Asbury

Senior Vice President and General Counsel

Mark joined ZS Pharma in July 2014 as Senior Vice President and General Counsel. Prior to ZS Pharma, Mark was the Vice President and General Counsel of Pharmacyclics, where he was responsible for all legal aspects of the corporation, including SEC matters, intellectual property, human resources and transactions. While there, he helped the company negotiate a \$975 million deal for its phase II molecule ibrutinib with Johnson & Johnson. Prior to that, Mark held a variety of positions at Genentech where he had broad exposure to all aspects of legal representation of a fully integrated pharmaceutical company, most recently as Associate General Counsel and Senior Director of Transactional Law. Prior to joining Genentech, Mark worked for the law firm of Shearman & Sterling, where he specialized in corporate finance, mergers and acquisitions and commercial debt financings.

Mark has a B.A. in Soviet Studies from Vanderbilt University and a J.D from Stanford Law School.

Risk to an Investment

We consider an investment in ZS Pharma to be a high-risk investment. ZS Pharma is a developmental stage company with no history of taking a treatment to market, and currently has no FDA approved products in its portfolio. The Company's products in development may fail in clinical trials or fail to be approved by the FDA or other regulatory agencies. Furthermore, early indications of efficacy do not necessarily translate into positive late-stage results. As with any company, ZS Pharma may be unable to obtain sufficient capital to fund planned development programs. Regulatory approval to market and sell a drug does not guarantee that the drug will penetrate the market, and sales may not meet the expectations of investors.

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