ZS Pharma (ZSPH)

ZS-9 is Poised to Change the Treatment of Hyperkalemia; Summary of KOL Event

On November 19th, ZS Pharma (NasdaqGM: ZSPH) hosted a Research and Development day that featured three Key Opinion Leaders (KOLs) from the specialties expected to prescribe ZS-9, Dr. Mikhail Kosiborod (Cardiologist), Dr. Bruce Spinowitz (Nephrologist), and Dr. Frank Peacock (Emergency Medicine). ZS-9 is being developed to treat hyperkalemia, or excess potassium, with NDA and MAA filings expected in the first half of 2015. Based on the compelling data set and presentations, we came away from the event especially impressed with ZS-9's rapid onset of action, tolerability profile, excellent control on low daily doses, and potential for ZS-9 to manage both acute and chronic cases of hyperkalemia, without the safety issues related to current treatments. There are approximately 4 million patients in the US with hyperkalemia, and we estimate that the market opportunity significantly exceeds $1 billion annually in the US alone.

- **Strong Clinical Data Package Supports Acute and Extended Hyperkalemia Treatment.** ZS Pharma has completed 3 clinical trials with its potassium (K^+) trap ZS-9, meeting the primary endpoints in all studies. The data consistently demonstrate ZS-9's ability to safely and rapidly lower serum K^+ levels and to maintain normokalemia, which is potassium of 3.5-5 mEq/L. In the most recent HARMONIZE trial, the median time to serum K^+ normalization was 2.2 hours. 84% and 98% of patients became normokalemic within 24 and 48 hours, respectively. In the subset of patients with serum K^+ >6 mEq/L, potassium levels were reduced by 0.5 mEq/L and 0.7 mEq/L at 1 and 2 hours, respectively, suggesting that ZS-9 may play a role in the emergent hospital and office settings. Additionally, 80% of patients on 5 g, 90% on 10 g, and 94% on 15 g of once daily ZS-9 were maintained in the normal range for 4 weeks. Two 1-year safety studies (ZS004e and ZS005) are ongoing. Company management noted that based on extensive discussions with US and European regulators, the completed studies should support a label that includes acute and extended treatment of hyperkalemia.

Expected Upcoming Milestones

- H1 2015 – Expected NDA & MAA submission for ZS-9 for the treatment of hyperkalemia.
- H1 2016 – Potential approval and commercial launch of ZS-9.

Analysts

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Market Data

Price	$42.96
Market Cap (M)	$894
EV (M)	$783
Shares Outstanding (M)	20.8
Fully Diluted Shares (M)	26.8
Avg Daily Vol	180,280
52-week Range:	$25.51 - $43.71
Cash (M)	$121.5
Net Cash/Share	$5.36
Annualized Cash Burn (M)	$40.0
Years of Cash Left	3.0
Debt (M)	$10.0
Short Interest (M)	1.90
Short Interest (% of Float)	9.1%

Financials

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

- **ZS-9 will be Revolutionary for the Acute Treatment of Hyperkalemia.** Dr. Frank Peacock, an emergency room physician at the largest ER in Houston, TX, discussed the treatment path for an average patient with acute hyperkalemia. His emergency department has extensive experience treating hyperkalemia and sees 30 hyperkalemic patients on a typical day. Most methods for managing serum potassium are temporary and patients ultimately require emergency dialysis. However, the availability of a safe and effective solution to reduce serum potassium *rapidly* could not only replace existing therapies, but also potentially eliminate the need for hospital admissions and emergency dialysis. As the agent with fast onset of action, ZS-9 would be very likely be the preferred agent in his hospital. Importantly, 50% of chronic hyperkalemia patients are first diagnosed in the hospital, representing an entry point for ZS-9 where patients receive initial treatment to normalize K^+ levels and then remain on long-term therapy to prevent future acute events.

- **Huge, Readily Accessible Market Opportunity.** Hyperkalemia occurs frequently in patients with chronic kidney disease, heart failure, and diabetes, and drugs that cause the body to retain potassium, most commonly RAAS inhibitors (ACEs, ARBs, and aldosterone antagonists). Based on the frequency of hyperkalemia in these populations, we estimate that there are 4 million patients in the US with chronic hyperkalemia. Given ZS-9's clinical profile, we expect it to be used as an alternative to *Kayexalate*, and even using conservative pricing and the capture of only *Kayexalate* used in hospitals, we believe sales for a branded acute hyperkalemia treatment could reach $300 million annually. Should these acute patients remain on ZS-9 for only a fraction of a year, the product could reach > $1 billion annually. The Company appears well positioned to pursue both the acute and chronic hyperkalemia markets.

- **ZS-9 HARMONIZE Data Published in *JAMA* Shows Significant Benefit for Heart Failure and Chronic Kidney Disease Patients.** Cardiologist Dr. Mikhail Kosiborod presented full results from ZS Pharma's Phase III (ZS004) study at the R&D/KOL event and at a late breaking session at the American Heart Association Scientific Meeting last weekend.[1] The results were also published in the *Journal of the American Medical Association*.[2] The trial enrolled 258 patients with hyperkalemia who were treated with 10 grams of ZS-9 three times per day during a 48 hour acute phase. Patients who achieved normokalemia were randomized to once daily ZS-9 (5, 10, or 15 grams) or placebo for 28 days as part of a randomized withdrawal period. Dr. Kosiborod also highlighted the diversity of patients included in the study. There was no upper limit for baseline serum K^+, no lower limit for estimated glomerular filtration rate (eGFR), and the study enrolled patients with many different co-morbidities such as heart failure (HF), chronic kidney disease (CKD), diabetes, and existing RAAS inhibitor use. The study results are described below.

  HARMONIZE Acute Phase Results

  - Mean baseline K^+ decreased from a baseline level of 5.6 mEq/L to 4.5 mEq/L ($p<0.0001$, change from baseline -1.1 mEq/L) at 48 hours, with statistically significant reductions in K^+ observed one hour after ZS-9 administration.
  - Median time to normokalemia was 2.2 hours with 84% of patients achieving normokalemia within 24 hours and 98% within 48 hours.
  - Patients with serum K^+ between 5.5 and <6.0 mEq/L (mean baseline of 5.7 mEq/L) and ≥6.0 mEq/L (mean baseline of 6.3 mEq/L) had reductions in mean serum K^+ of -0.3 mEq/L and -0.5 mEq/L at 1 hour and -0.4 mEq/L and -0.7 mEq/L at 2 hours, respectively, suggesting a potential for use in acute settings that will warrant further investigation.
  - The results were consistent across all pre-specified disease subgroups and patients on RAAS inhibitor therapy.
  - The most common adverse events during the acute phase of treatment were diarrhea (1.2%), as well as constipation, dizziness, and nausea (all 0.8%).

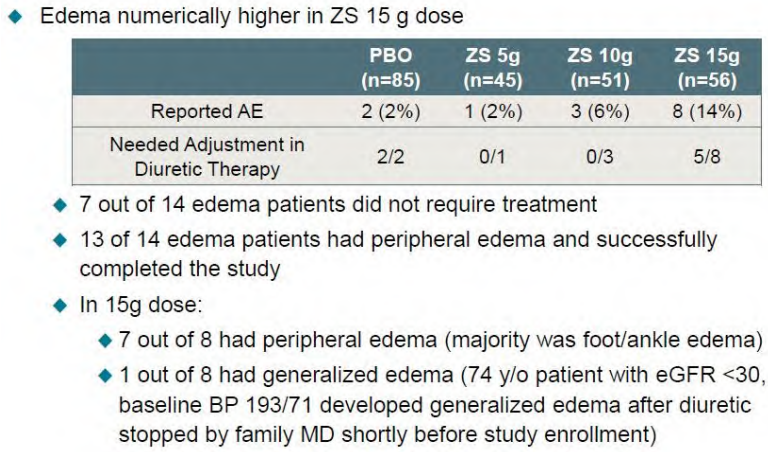
  HARMONIZE 28-Day Double-Blind Randomized Withdrawal Phase

  - HARMONIZE met the primary efficacy endpoint: mean serum K^+ levels were significantly lower with all three doses of ZS-9 versus placebo (placebo – 5.1 mEq/L, 5 g – 4.8 mEq/L, 10 g – 4.5 mEq/L, 15 g – 4.4 mEq/L, $p<0.0001$ all doses).
  - Maintenance of normokalemia was more frequent in the ZS-9 treated groups than in the placebo group, with a significantly higher proportion of patients having mean serum K^+ < 5.1 mEq/L between days 8-29 (placebo – 46%, 5 g – 80%, 10 g – 90%, 15 g – 94%, $p<0.001$ all doses).

ZS-9 appeared to be well tolerated.

- The incidence of urinary tract infections was low with one case reported in each of the placebo (1.2%), 5 g (2.2%), and 15 g (1.8%) groups and no reported cases in the 10 g group.
- There were six cases of constipation on placebo (7.1%) compared to no cases on 5 g, one case on 10 g (2.0%), and one case on 15 g (1.8%).
- There were five cases of hypokalemia on 10 g (9.8%) and six cases on 15 g (10.7%) compared to no cases on both placebo and 5 g. All cases of hypokalemia were transient, mild (3.0 to 3.4 mEq/L), and resolved after the dose of ZS-9 was reduced from daily to every other day (per protocol) for the remainder of the study.
- There were 14 cases of edema, as shown in **Figure 1**: two cases of edema on placebo (2.4%), one case on the 5 g dose (2.2%), three cases on 10 g (5.9%), and eight cases on 15 g (14.3%). Seven cases of edema resolved or did not require treatment during study (one case on 5 g, all three cases on 10 g, and three cases on 15 g). Of the 14 patients with edema, 13 completed the study.

Figure 1. Edema Cases Reported in HARMONIZE

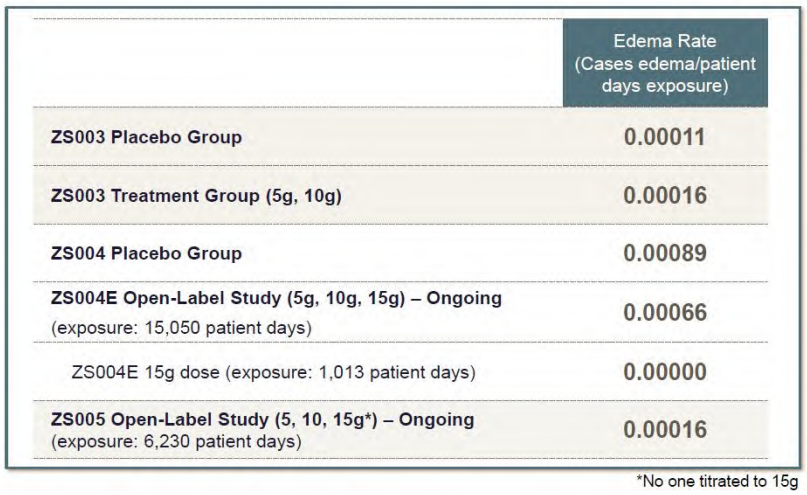


Source: Company Reports

- **Excellent Safety Profile Supports Approval.** Dr. Kosiborod also presented safety data from trial ZS004, reporting a tolerability profile similar to placebo and no treatment-related serious adverse events. He provided additional information on the rates of edema observed in the completed and ongoing long-term ZS trials (ZS002, ZS003, ZS004/HARMONIZE, ZS004e, and ZS005), which suggest that the higher rate of edema in the 15 g group was a result of the higher prevalence of sicker patients in the 15 g dose group. The data are shown in **Figure 2**. Most convincing were the fact that the long-term ZS004e and ZS005 studies have a lower rate of edema than the placebo group in the ZS004 study, and the fact that no edema has occurred in any patient in ZS004e on the 15 g dose despite months of therapy.

  Consistent with the strong safety and tolerability observed in ZS004, ZS Pharma CEO Robert Alexander announced new toxicology data clearly showing that ZS-9 is not systemically absorbed. Dogs treated for 9 months had no ZS-9 in their urine despite assay sensitivity at the parts per billion level. Similarly, there was no ZS-9 detected in human samples collected in ZS004 again despite assay sensitivity at the parts per billion level. Overall the data show that ZS-9 has an excellent safety and tolerability profile.

Figure 2. Edema Rate Across Phase III ZS-9 Trials



	Edema Rate (Cases edema/patient days exposure)
ZS003 Placebo Group	0.00011
ZS003 Treatment Group (5g, 10g)	0.00016
ZS004 Placebo Group	0.00089
ZS004E Open-Label Study (5g, 10g, 15g) – Ongoing (exposure: 15,050 patient days)	0.00066
ZS004E 15g dose (exposure: 1,013 patient days)	0.00000
ZS005 Open-Label Study (5, 10, 15g*) – Ongoing (exposure: 6,230 patient days)	0.00016

*No one titrated to 15g

Source: Company Reports

- **Hyperkalemia Limits RAAS Use.** Given the demographics and comorbidities, the HARMONIZE trial provides a view of how ZS-9 performs in different patients. ZS-9 displayed similar activity in all subpopulations, confirming its real-world potential as a hyperkalemia treatment. Dr. Bruce Spinowitz, a Nephrologist who was also an investigator in patiromer's Phase III study, discussed the high frequency that medications such as RAAS inhibitors disrupt the body's K^+ balance and trigger hyperkalemia, and the role that ZS-9 could play in this setting. We estimate that 1.4 million CKD and HF patients would benefit from a K^+ control agent to enable therapeutic doses of cardio-protective RAAS inhibitor therapy. This represents a staggering multi-billion dollar opportunity.

- **High Level of Control with Once Daily 5 g and 10 g Suggests These Doses Will be Used for 90% of Patients.** Based on the data presented and comments from management on the level of titration observed in the ongoing long-term studies (ZS004e and ZS005) where patients are allowed to titrate, the once daily 5 g and 10 g doses will be the most commonly used, with 15 g required in <10% of patients. The low doses levels provide additional differentiation and augment the COGS advantages of ZS-9.

- **ZS-9 Could Become the Standard of Care Despite a Head Start for Patiromer.** Relypsa (NasdaqGS: RLYP) is developing a competing product for hyperkalemia, patiromer, which is an organic polymer that exchanges calcium ions (Ca^{2+}) for K^+. Relypsa recently filed an NDA for patiromer. There are several features of ZS-9 that set it apart from patiromer and could make it the standard of care:

  - **Rapid onset of action:** Median time to normalization 2.2 hours and statistically significant reduction in serum potassium by 1 hour for ZS-9 compared to 7 hours for patiromer (median time to normalization unknown).
  - **High Response Rates:** >98% of patients normalized within 48 hours with ZS-9 compared to approximately 20% at 48 hours for patiromer.
  - **Convenient dosing**: ZS-9 is a once daily treatment for maintenance of hyperkalemia compared to twice daily for patiromer.
  - **Strong tolerability profile**: The rate of GI side effects from ZS-9 is similar to placebo compared to higher rates of diarrhea, constipation, and nausea for patiromer.
  - **High ion selectivity**: ZS-9 is highly selective for potassium whereas patiromer can non-specifically bind other ions including magnesium.

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