ZS Pharma (ZSPH)

Survey of Cardiologists Highlights Potential $1.5-2.9 Billion Opportunity for ZS-9 in Hyperkalemia

We conducted a survey of 63 general cardiologists to estimate the market potential for ZS Pharma's (NasdaqGM: ZSPH) ZS-9 as a chronic treatment for hyperkalemia in the cardiology setting. The results build on our prior analysis of the opportunity in the nephrology setting. The survey suggests that the annual US market potential for ZS-9 as a chronic hyperkalemia therapy for patients treated by cardiologists could be as much as $1.5-2.9 billion. We estimate that the combined market opportunity between cardiologists and nephrologists for chronic therapy could reach $4.5-5.9 billion per year in the US.

- **Survey Rationale.** The two major patient populations who may benefit from ZS Pharma's hyperkalemia candidate ZS-9 are those with chronic kidney disease (CKD), who are treated by nephrologists, and those with heart failure (HF), who are treated by cardiologists. We previously conducted a nephrologist survey to address the CKD market and have published the results. Our new survey of general cardiologists attempts to address the HF market.
- **Key Results from the Survey:** Below are the three most important findings from our analysis of the survey data:
  - An estimated 1.3 million patients per year in the US, treated by cardiologists, would benefit from chronic therapy with an agent such as ZS-9, translating into a $1.5-2.9 billion opportunity.
  - There are between 570,000 and 1.3 million hyperkalemia patients per year in the US that see a cardiologist in the office setting.
  - Approximately 500,000 to 1.2 million patients per year in the US who are treated by cardiologists have a strong incentive to chronically manage hyperkalemia so that they can maintain adequate doses of RAAS inhibitor therapy.

Expected Upcoming Milestones

- Q2 2015 – Expected NDA submission for ZS-9 for the treatment of hyperkalemia.
- H2 2015 – Expected MAA submission for ZS-9 for the treatment of hyperkalemia.
- 2015 – Potential updates from long-term studies ZS004e and ZS005.
- H1 2016 – Potential approval and commercial launch of ZS-9.

Risk to Invesment

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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Market Data

Price	$48.99
Market Cap (M)	$1,225
EV (M)	$975
Shares Outstanding (M)	25.0
Fully Diluted Shares (M)	29.8
Avg Daily Vol	320,466
52-week Range:	$25.51 - $52.80
Cash (M)	$259.6
Net Cash/Share	$9.98
Annualized Cash Burn (M)	$40.0
Years of Cash Left	>5.0
Debt (M)	$10.0
Short Interest (M)	2.34
Short Interest (% of Float)	14.0%

Financials

FY Dec		2013A	2014A	2015A
EPS	Q1	NA	(6.60)A	(1.05)A
	Q2	(4.81)A	(4.72)A	NA
	Q3	(6.14)A	(0.81)A	NA
	Q4	NA	NA	NA
	FY	(21.84)A	(5.47)A	NA

For analyst certification and disclosures please see page 9

- **Survey Data Suggest a Market Potential of $1.5-2.9 Billion for Chronic Therapy with ZS-9 in the Cardiology Setting.** Based on question #8 of our survey we constructed a bottom-up estimate of the potential market opportunity for ZS-9 in the chronic treatment setting. Worth noting is that this estimate does not include those treated by nephrologists, who represent a separate and additional market opportunity that we explored in a prior note. As shown in **Figure 1,** cardiologists reported that on average 13 patients per month in their office practice, or approximately 156 patients per year, could benefit from a non-absorbable compound with ZS-9's profile. The top, bold entry came directly from our survey. Assuming these numbers are representative of the total general cardiologist specialty, there are approximately 2.6 million total patients each year in the US who are treated by cardiologists and could benefit from an agent such as ZS-9.

Figure 1. Market Potential for ZS-9 in Patients Treated by General Cardiologists

Average # of patients per month in the office setting that could benefit from a non-absorbable agent	**13**
Average # of patients per year that could benefit from a non-absorbable agent	156
Number of general cardiologists in the US	16,500
Total patients seen by general cardiologists per year in US that could benefit from a non-absorbable agent	2.6 million
Potential overlap with nephrologists	50%
Total patients seen by general cardiologists per year in US, not treated for hyperkalemia by a nephrologist, that could benefit from a non-absorbable agent	1.3 million
Patients likely to receive treatment (33-50% penetration)	425,000-640,000
Estimated price per month	$600
Compliance over 12 months	50-75%
Market opportunity	**$1.5-2.9 billion**

Source: LifeSci Capital

Due to the high rate of co-morbidities among patients treated by cardiologists, many of these patients also see nephrologists, who may intervene with a hyperkalemia treatment. Based on our follow-up discussions with surveyed cardiologists, we estimate that about 50% of their patients could receive hyperkalemia treatment from a nephrologist. We assumed a penetration rate of 33-50%, an estimated price of $600 per month, and a compliance rate of 50-75% across 12 months of potential therapy. The compliance range is in line with treatment adherence to RAAS inhibitors.[1,2] In total the market opportunity for a non-absorbable agent like ZS-9 as a chronic treatment in

[1] Vegter, S. et al., 2011. Compliance, persistence, and switching patterns for ACE inhibitors and ARBs. *The American Journal of Managed Care*, 17(9), pp609-616.

the general cardiologist office setting is approximately $1.5-2.9 billion per year in the US.

- **Hyperkalemia Population Estimate from Survey Larger than Top-down Approximation.** We took our survey data and constructed a simple bottom-up estimate for the total number of hyperkalemia patients seen by general cardiologists per year in the US. This was compared to a top-down, population-based analysis. As shown in **Figure 2**, surveyed cardiologists reported that on average they see 13 patients per month, or approximately 156 per year with hyperkalemia. The bolded entry came directly from our survey. This leads to approximately 1.3 million hyperkalemia patients that visit general cardiology offices each year in the US. Having hyperkalemia does not necessarily indicate the need for treatment, which is why we performed the analysis in the prior figure to estimate the patients who may benefit from chronic therapy. In the case of this survey the numbers were similar, which may represent a greater desire by cardiologists to maintain patients on guideline recommended doses of RAAS inhibitor therapy via the use of a chronic hyperkalemia treatment.

For our top-down analysis, shown on the right of the figure, we started with the estimated number of heart failure patients in the US in 2008, which was derived from the American Heart Association's 2012 heart disease and stroke statistics analysis. Approximately 20% of patients receiving an ACE inhibitors or ARB have hyperkalemia defined as serum potassium above 5.0 mEq/L.

Figure 2. Size of Hyperkalemia Market Treated by General Cardiologists

Survey Data		Top-down Analysis	
Average # of hyperkalemia patients (>5.0 mEq/L) per month	**13**	Number of heart failure patients[3]	5.7 million
Average # of hyperkalemia patients treated by a general cardiologist per year	156	Percentage of patients with hyperkalemia[4]	20%
Estimated number of general cardiologists in the US	16,500	Total patients with heart failure and hyperkalemia	1.1 million
Total chronic hyperkalemia patients seen by general cardiologists per year in US	2.6 million	-	-
Potential overlap with nephrologists	50%	Potential overlap with nephrologists	50%
Total chronic hyperkalemia patients seen exclusively by general cardiologists per year in US	1.3 million	Total chronic hyperkalemia patients seen exclusively by general cardiologists per year in US	570,000

Source: LifeSci Capital

[2] Lamb, D.A. et al., 2008. Adherence to beta-blockers and ACE inhibitors/angiotensin receptor blockers in the first year after diagnosis of heart failure: 10 year observational trends. *Circulation,* 118, s1093.
[3] 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.
[4] 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(3), pp547-552.

The number of estimated hyperkalemia patients is different between our bottom-up and top-down analyses. It is worth noting that our top-down estimate for the percentage of patients with hyperkalemia is derived from patients who are taking at least one RAAS inhibitor. HF patients have the potential to develop hyperkalemia in the absence of RAAS inhibitor therapy, and this or other factors may account for the discrepancy.

- **Patients on RAAS Inhibitors Remain the Target Population for ZS-9 in the Chronic Treatment Setting.** RAAS inhibitors, 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 RAAS inhibitor therapy. The cardiologists we interviewed were interested in maintaining patients on adequate levels of RAAS inhibitors, and reported that some patients are actually prohibited from taking certain RAAS inhibitors due to prior hyperkalemia. This suggests that patients who are receiving RAAS inhibitors, and especially those on lower than guideline recommended doses, are prime candidates for long-term hyperkalemia treatment. In **Figure 3** we show a bottom-up analysis using two different survey questions to estimate this patient population, and also included a top-down analysis.

Figure 3. Number of Hyperkalemic Patients with a Strong Incentive for Treatment

Survey Results				Existing Data	
Total hyperkalemia patients (>5.0 mEq/L) seen by general cardiologists per year in US	1.3 million	**Average # of patients per month on lower than optimal guideline recommended RAAS inhibitor doses due to hyperkalemia or concerns of hyperkalemia**	**12**	Number of heart failure patients	5.7 million
Percentage of hyperkalemia cases in patients receiving RAASi's or exacerbated by RAASi's	**85%**	Average # of patients per year on lower than optimal guideline recommended RAAS inhibitor doses due to hyperkalemia or concerns of hyperkalemia	144	Percentage of patients are taking at least one RAAS inhibitor[5,6,7,8,9]	50%
Potential overlap with nephrologists	Accounted for above	Potential overlap with nephrologists	50%	Potential overlap with nephrologists	50%
-	-	Number of general cardiologists in the US	16,500	Percentage of patients on suboptimal RAAS inhibitor dose[10,11,12]	66%
-	-	-	-	Percentage of patients on suboptimal dose due to hyperkalemia[13]	50%
Patients with strong incentive to manage hyperkalemia	1.1 million	Patients with strong incentive to manage hyperkalemia	1.2 million	Patients with strong incentive to manage hyperkalemia	0.5 million

Source: LifeSci Capital

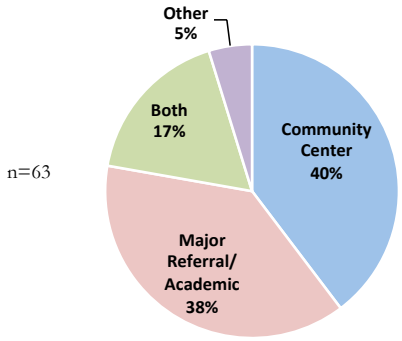
These three estimates indicate that approximately 500,000 to 1.2 million hyperkalemia patients each year in the US and have a strong incentive to manage their disease, or their cardiologist has a strong interest in managing their disease. Using this patient estimate and similar assumptions that were used in **Figure 1**, the annual US market potential for an agent such as ZS-9 is approximately $600 million to $2.9 billion in the general cardiology setting.

[5] 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.
[6] 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.
[7] Masoudi, F.A. et al., 2005. The Complexity and Cost of Drug Regimens of Older Patients Hospitalized With Hearth Failure in the United States. *Arch Intern Med*, 165, pp2069-2076.
[8] DiMartino, L.D. et al., 2010. Use of Guideline-Recommended Therapies for Heart Failure in the Medicare Population. *Clin. Cardiol*, 33(7), pp400-405.
[9] Lachaine, J. et al., 2011. Use, tolerability and compliance of spironolactone in the treatment of heart failure. *BMC Clinical Pharmacology*, 11(4).
[10] 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.
[11] 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.
[12] 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.
[13] Ahuja, T.S. et al., 2000. Predictors of the development of hyperkalemia in patients using Angiotensin-Converting Enzyme inhibitors. *American Journal of Nephrology*, 20, pp268-272.

- **Study Design and Full Results.** We surveyed 63 general cardiologists and asked them to complete a questionnaire outlining their experience with hyperkalemia patients, as well as to understand their view of the utility for a non-absorbable compound with ZS-9's profile. **Figure 4** shows the survey design and a summary of the results.

Figure 4. General Cardiologist Survey Design and Results

1. Please describe your practice.



2. How many patients per month do you treat in your office practice?

Average = 277/month; n=59

3. How many patients per month in your office practice have hyperkalemia (serum potassium levels >5.0 mEq/L.)?

Average = 13/month; n=59

4. Use of RAAS inhibitors can increase serum potassium and is commonly linked with hyperkalemia. How many patients per month in your office practice with hyperkalemia are on RAAS inhibitor therapy?

Average = 11/month; n=56

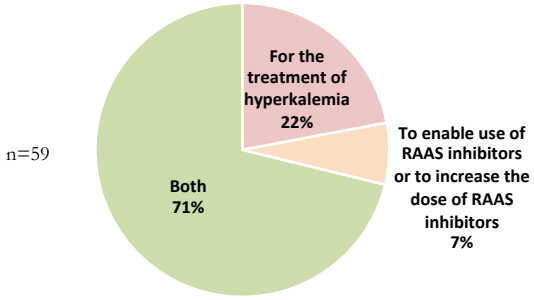
5. How many patients per month in your office practice are on lower than optimal guideline recommended RAAS inhibitor doses due to hyperkalemia or concerns of hyperkalemia?

Average = 12/month; n=58

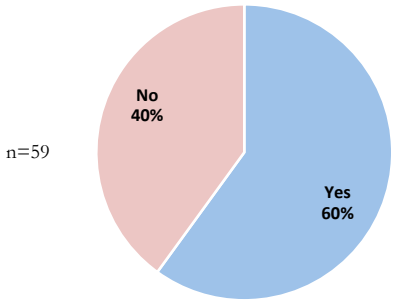
Background information: A non-absorbable compound is being developed for hyperkalemia in both the acute and long-term maintenance settings. Recent Phase III data published in leading medical journals indicate that the agent can rapidly reduce serum potassium and maintain normokalemia. The median time to normalization of serum potassium is 2.2 hours and >98% of patients are normalized within 48 hours of treatment.

Once daily dosing of 5-10 grams of this agent is used for maintenance. This dose can help patients maintain serum potassium levels of 4.6 mEq/L regardless of the dose of RAAS medication. Patients on the non-absorbable compound also saw 30% reductions in serum aldosterone levels. The overall adverse event (AE) and gastrointestinal AE profile is similar to placebo.

6. In which situations would you use the non-absorbable compound?



7. Are you aware that elevated serum potassium leads to increased aldosterone levels and that elevated potassium levels can increase renal and cardiovascular fibrosis?



8. In total, how many patients per month do you have that would benefit from treatment with a non-absorbable compound?

Average = 13/month; n=57

Source: LifeSci Capital

An overview of the survey results is below:

- **#1:** 40% and 38% of the respondents categorized their practice as a community center or major referral/academic center, respectively. The remaining physicians were part of a mixed major/referral/academic/community center or some other center type.
- **#2:** The general cardiologists reported seeing on average 277 patients per month in their office practice.
- **#3:** The general cardiologists reported seeing on average 13 hyperkalemia patients per month, or roughly 5% of their total office practice.
- **#4:** The general cardiologists reported seeing on average 11 hyperkalemia patients per month who are on RAAS inhibitor therapy or their condition is exacerbated due to RAAS inhibitors. This suggests that on average approximately 85% of hyperkalemia patients are receiving RAAS inhibitors.
- **#5:** On average, the general cardiologists see 12 patients per month who are on lower than optimal guideline recommended RAAS inhibitor doses due to hyperkalemia or concerns of hyperkalemia.
- **#6:** The previous point is validated by 71% of participants reporting that they would use a non-absorbable agent to treat hyperkalemia, and enable use of RAAS inhibitors or to increase the dose.
- **#7:** 60% of cardiologists were aware that elevated serum potassium can increase aldosterone levels and that elevated serum potassium can increase renal and cardiovascular fibrosis.
- **#8:** The cardiologists reported seeing on average 13 patients per month who may benefit from a non-absorbable agent for hyperkalemia.

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