ZS Pharma (ZSPH)

Survey of Nephrologists Highlights Potential $3 Billion Opportunity for ZS-9 in Hyperkalemia

We conducted a survey of 76 nephrologists to estimate the market potential for ZS Pharma's (NasdaqGM: ZSPH) ZS-9 as a treatment for hyperkalemia in the chronic setting. Our survey results suggest that the market potential for ZS-9 as a chronic therapy for patients treated by nephrologists is as much as $3 billion per year in the US. The results are in line with other estimates of the market and highlight the potential of ZS-9 to generate revenues in excess of $1 billion.

- **Survey Rationale.** ZS Pharma is developing ZS-9 for the treatment of excess serum potassium, known as hyperkalemia, and is expected to file for approval in the US in the second quarter of 2015. The clinical data supporting ZS-9's approval indicate that it has a median time to normalization of 2 hours, and 80-94% of patients were controlled in long-term studies. With an FDA decision anticipated in 2016, the focus has shifted to the potential commercial opportunity for ZS-9.

  The current treatments for hyperkalemia only offer temporary relief or are associated with tolerability issues that limit long-term use. This means that if approved ZS-9 will enter a new, unserved market with clear unmet need. Top-down estimates starting with the number of CKD patients in the US have typically indicated that nephrologists treat approximately 2 million patients with hyperkalemia each year. Our current survey of nephrologists provides a bottom-up estimate for the patient size and market opportunity for ZS-9 in the chronic setting.

- **Key Results from the Survey:** Below are three key results from our analysis of the survey data. We note that the estimates are for patients treated exclusively by nephrologists, and does not include patients with heart failure treated by cardiologists.
  - An estimated 1.24 million patients per year in the US would benefit from chronic therapy with an agent such as ZS-9, translating into a $3 billion market opportunity.
  - There are between 1.6 and 1.8 million hyperkalemia patients per year in the US that see a nephrologist in the office setting. Many of these patients could benefit from chronic therapy.
  - Approximately 1 million patients per year in the US 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.

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Market Data

Price	$41.66
Market Cap (M)	$1,062
EV (M)	$772
Shares Outstanding (M)	25.5
Fully Diluted Shares (M)	30.3
Avg Daily Vol	283,393
52-week Range:	$25.51 - $52.80
Cash (M)	$300.0
Net Cash/Share	$11.37
Annualized Cash Burn (M)	$40.0
Years of Cash Left	>5.0
Debt (M)	$10.0
Short Interest (M)	2.20
Short Interest (% of Float)	13.0%

cash is pro forma

Financials

FY Dec		2012A	2013A	2014A
EPS	Q1	NA	NA	NA
	Q2	NA	(4.81)A	(4.72)A
	Q3	NA	(6.14)A	(0.81)A
	Q4	NA	NA	NA
	FY	(6.74)A	(21.84)A	(5.47)A

- **Survey Data Suggest a Market Potential Near $3 Billion for Chronic Therapy with ZS-9.** We extrapolated the data from question #7 of our survey to provide 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 cardiologists, who represent a separate and additional market opportunity. As shown in **Figure 1,** nephrologists reported that on average 23 patients per month, or approximately 276 patients per year, could benefit from a non-absorbable compound with ZS-9's profile. The top entry is bolded to indicate that it came directly from our survey. An estimated 50% of the hyperkalemia patients are seen in the office setting. Assuming these numbers are representative of the total nephrologist specialty, there are approximately 1.24 million patients each year in the US who could benefit from an agent such as ZS-9. We assumed a penetration rate of 50%, an estimated price of $600 per month, and a compliance rate of 75% across 12 months of potential therapy. In total the market opportunity for a non-absorbable agent like ZS-9 as a chronic treatment in the nephrologist office setting is approximately $3 billion per year in the US.

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

Average # of patients per month that could benefit from a non-absorbable agent	**23**
Average # of patients per year that could benefit from a non-absorbable agent	276
Average # of patients per year that are candidates for chronic therapy with a non-absorbable agent (50%)	138
Number of active nephrologists engaged in direct patient care[1]	9,000
Total patients seen by nephrologists per year in US that could benefit from a non-absorbable agent	1.24 million
Patients likely to receive treatment (50% penetration)	621,000
Estimated price per month	$600
Compliance over 12 months	75%
Market opportunity	**$3 billion**

Source: LifeSci Capital

- **Hyperkalemia Population Estimate from Survey is in Line with a Top-down Approximation.** We took our survey data and constructed a simple bottom-up estimate for the total number of hyperkalemia patients seen by nephrologists per year in the US. This was validated by comparison to a top-down, population and epidemiological-based analysis. As shown in **Figure 2**, surveyed nephrologists reported that on average they see 29 patients per month, or approximately 350 per year with hyperkalemia. The top left entry is bolded to indicate that it came directly from our survey. An estimated 50% of the hyperkalemia patients are seen in the office setting. Assuming these numbers are representative of the total nephrologist specialty, it would amount to approximately 1.6 million hyperkalemia patients that visit nephrologist 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.

For our top-down analysis, shown on the right of the figure, we started with the estimated number of Stage 3 and 4 CKD patients in the US in 2000, which was derived from a >13,000 patient database from the National Health and Nutrition Examination Surveys. The number was adjusted to account for the 9.7% increase in US population between 2000 and 2010 based on the US census. Approximately

36% and 11% of Stage 3 and Stage 4 CKD patients, respectively, have hyperkalemia defined as serum potassium ≥5.5 mEq/L. About 30% will see a nephrologist within 1 year of diagnosis, resulting in 1.8 million hyperkalemia patients seen by nephrologists per year in the US.

Figure 2. Size of Hyperkalemia Market Treated by Nephrologists

Survey Data		Top-down Analysis	
Average # of hyperkalemia patients (>5.0 mEq/L) per month	**29**	Number of Stage 3 and 4 CKD patients in 2000[2]	16.2 million
Average # of hyperkalemia patients treated by a nephrologist per year	348	Number of Stage 3 and 4 CKD patients adjusted to 2010	17.8 million
Fraction of patients who are candidates for chronic therapy (50%)	174	Number of Stage 3 and 4 CKD patients with serum potassium ≥5.5 mEq/L[3]	6.1 million
Number of active nephrologists engaged in direct patient care	9,000	Percentage of patients who will see a nephrologist within 12 months of diagnosis[4]	~30%
Total chronic hyperkalemia patients seen by nephrologists per year in US	1.6 million	Total chronic hyperkalemia patients seen by nephrologists per year in the US	1.8 million

Source: LifeSci Capital

Despite some differences between the two methods such as the focus on CKD and a higher threshold for defining hyperkalemia in the top-down analysis, the two estimates are largely in line with one another and suggest a large market of chronic hyperkalemia patients being treated by nephrologists.

- **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. We did follow up calls with certain survey respondents, and the nephrologists we spoke to stressed the importance of maintaining patients on adequate levels of RAAS inhibitors, and the difficulty posed by routinely having to adjust doses to avoid 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 nephrologists per year in US	1.6 million	**Average # of patients per month on lower than optimal guideline recommended RAAS inhibitor doses due to hyperkalemia or concerns of hyperkalemia**	**21**	Top-down analysis of late-stage CKD patients with hyperkalemia (>5.5 mEq/L)	1.8 million
-	-	Fraction of patients who are candidates for chronic therapy (50%)	10.5	-	-
Percentage of hyperkalemia cases in patients receiving RAASi's or exacerbated by RAASi's	**53%**	Average # of patients per year on lower than optimal guideline recommended RAAS inhibitor doses due to hyperkalemia or concerns of hyperkalemia	126	Percentage of hyperkalemia patients receiving a RAASi within 12 months of CKD diagnosis[5]	50-60%
-	-	Number of active Nephrologists engaged in direct patient care	9,000	-	-
Patients with strong incentive to manage hyperkalemia	0.8 million	Patients with strong incentive to manage hyperkalemia	1.1 million	Patients with strong incentive to manage hyperkalemia	1 million

Source: LifeSci Capital

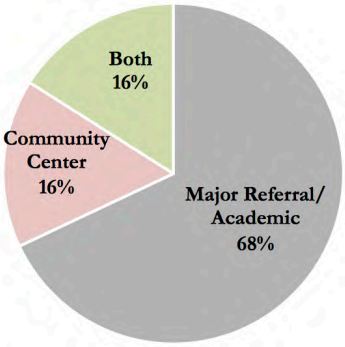
These three estimates indicate that approximately 1 million hyperkalemia patients are seen by nephrologists each year in the US and have a strong incentive to manage their disease, or their physician has a strong interest in managing their disease. Using this patient estimate and similar assumptions that were used in **Figure 1**, the market potential for an agent such as ZS-9 is approximately $2.4 billion in the nephrology setting per year in the US.

- **Study Design and Full Results.** We surveyed 76 nephrologists 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. Nephrologists Survey Design and Results

1. Please describe your practice.

n=75



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

Average = 29/month; n=73

3. What percentage of the hyperkalemia cases occur in patients on RAAS inhibitor therapy or is exacerbated by RAAS inhibitors?

Average = 53%; n=73

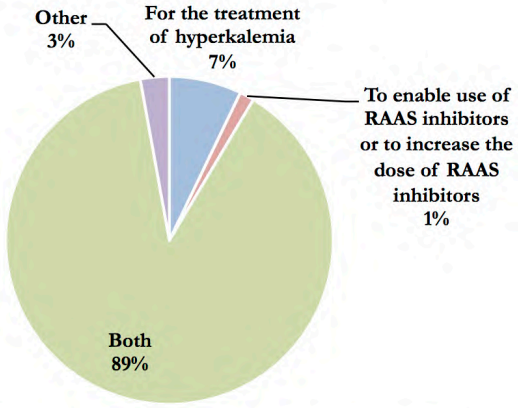
4. How many patients per month in your practice are on lower than optimal guideline recommended RAAS inhibitor doses due to hyperkalemia or concerns of hyperkalemia?

Average = 21/month; n=72

Background information: A non-absorbable compound is being developed for hyperkalemia in both the acute and long-term maintenance settings. Recent Phase III data in leading medical journals indicate that it 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 the agent is used for maintenance and controls potassium levels at 4.6 mEq/L regardless of the dose of RAAS medication. Patients on the non-absorbable compound also saw a 2-3 mEq/L increase in bicarbonate levels with 70% of patients with low bicarbonate levels returning to the normal range. The overall adverse event (AE) and gastrointestinal AE profile is similar to placebo.

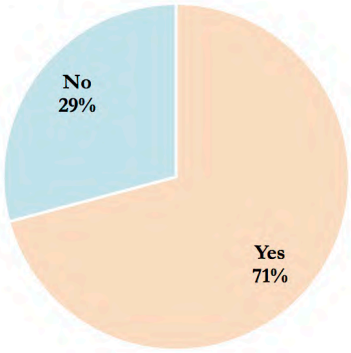
5. In which situations would you use the non-absorbable compound?

n=70



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

n=72



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

Average = 23/month; n=70

Source: LifeSci Capital

An overview of the survey results is below:

#1: More than two-thirds of the respondents categorized their practice as a major referral or academic center. The remaining physicians were split between community centers and a mix of both center types.

#2: The nephrologists reported seeing on average 29 hyperkalemia patients per month, and that approximately 50% of these patients are seen in the office setting and are candidates for chronic therapy.

#3: The nephrologists reported that on average, 53% of hyperkalemia patients are on RAAS inhibitor therapy or their condition is exacerbated due to RAAS inhibitors.

#4: On average, the nephrologists see 21 patients per month who are on lower than optimal guideline recommended RAAS inhibitor doses due to hyperkalemia or concerns of hyperkalemia. Based on our discussions with nephrologists, these patients are prime candidates for chronic hyperkalemia treatment to enable more stable or larger doses of RAAS inhibitors.

#5: The previous point is validated by 89% 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.

#6: 71% of nephrologists were aware that elevated serum potassium can increase aldosterone levels and that elevated serum potassium can increase renal and cardiovascular fibrosis.

#7: The nephrologists reported seeing on average 23 patients per month who may benefit from a non-absorbable agent for hyperkalemia, and approximately 50% of these patients are seen in the office setting and are candidates for chronic therapy.

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