William Blair

ZS Pharma, Inc.

November 20, 2014

Analyst Event Provides Clarity on Edema, Reaffirms Comprehensive Clinical Program, and Best-in-Class Profile

- We attended ZS Pharma's analyst event in New York City on Wednesday, November 19. At the event, the company went into further detail regarding the results from the second pivotal Phase III study (HARMONIZE) for its lead candidate, ZS-9, that were presented at the annual meeting of the American Heart Association on Monday, November 17, and published in the *Journal of the American Medical Association*. Below we present our key conclusions and additional details from the event.
- **ZS-9 is broadly efficacious in patients with hyperkalemia, regardless of underlying etiologies.** The company's chief medical officer, Dr. Henrik Rasmussen, presented data from the broad program of completed clinical trials to date: ZS002 in 90 patients, ZS003 in 738 patients, and ZS004 in 237 patients. All trials consisted of an initial 48 hour induction phase where patients were dosed with 10 grams of ZS-9 three times a day, where normokalemia was achieved in 98% of patients, regardless of underlying etiology and mean serum potassium at baseline. Furthermore, the median onset-of-action was 2.2 hours, which we believe is a significant differentiating factor from the combination of therapies used to manage hyperkalemia crises in the acute setting and the competitive development stage product, patiromer. In the maintenance phase of HARMONIZE, all doses of ZS-9 tested (5 g, 10 g, and 15 g) showed significantly lower serum potassium at day 29 of therapy, with patients who presented with various baseline levels becoming normokalemic. Lastly, as shown in exhibits 1 and 2, additional beneficial effects, which have not previously been described, included the positive effect of ZS-9 on bicarbonate and aldosterone levels. These data reduce concerns surrounding the potential for acidosis in diabetics and chronic kidney disease patients, respectively. We believe competitors had been discussing these potential side effects of ZS-9, although data presented at the event clearly refutes these concerns.
- **The concerns over the adverse event profile (particularly edema in the 15 g dose) in the HARMONIZE study are overblown.** The company addressed the concerns over edema in the 15 gram dose head on, with Dr. Mikhail Kosiborod providing an in-depth analysis of results from ZS002 and ZS003 in addition to newly released up-to-date results from the ZS004 extension study and ZS005 studies. As shown in exhibit 3, edema rate (defined as cases of edema divided by the number of patient days' exposure) was lower in the retrospective analysis of ZS003 with a placebo rate of 0.00011 and the ZS003 treatment groups (both 5 g and 10 g doses) of 0.00016. In the ZS004 extension study, the placebo rate was 0.00066; however, the 15 g dose exposure edema rate in the ZS004 extension study (1013 patient days) was 0.00000, also lower than placebo arm. The ZS005 open-label edema rate to date (6230 patient days) was 0.00016 with no patients currently titrated to the 15 g dose. In addition, 7 out of 14 patients did not require any treatment adjustment, and of the patients with edema, 7 out of 8 had relatively mild peripheral edema (the majority being foot/ankle edema). We continue to believe that the edema rate seen in the HARMONIZE results was due to an artifact seen as a result of randomization in the study where patients in the 15 g dose (exhibit 4) included patients with more advanced chronic kidney disease (lower glomerular filtration rate), and increased brain natriuretic peptide (a marker for increased chronic cardiovascular disease).

ZS Pharma is a specialty pharmaceutical company located in San Mateo, California, focused on developing therapies based on highly selective ion trap chemistry.

Tim Lugo
+1 415 248 2870
tlugo@williamblair.com

Raju Prasad, Ph.D.
+1 312 364 8469
rprasad@williamblair.com

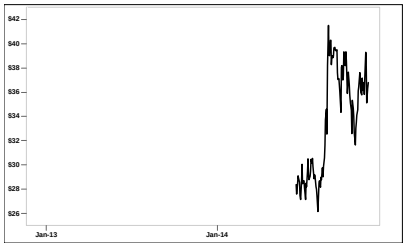
Stock Rating:	**Outperform**
Company Profile:	**Aggressive Growth**
Price Target:	$75.00
Symbol:	ZSPH (NASDAQ)
Price:	$37.33 (52-Wk.: $26-$43)
Market Value (mil.):	$777
Fiscal Year End:	December
Long-Term EPS Growth Rate:	
Dividend/Yield:	None

	2013A	2014E	2015E
Estimates			
EPS FY	$-8.52	$-3.28	$-2.96
CY		$-3.28	$-2.96
Valuation			
FY P/E	NM	NM	NM
CY P/E		NM	NM

Trading Data (FactSet)	
Shares Outstanding (mil.)	3
Float (mil.)	9
Average Daily Volume	140,465

Financial Data (FactSet)	
Long-Term Debt/Total Capital (MRQ)	0.0
Book Value Per Share (MRQ)	6.2
Return on Equity (TTM)	-235.2

Two-Year Price Performance Chart



Sources: FactSet, William Blair & Company estimates

- **In our opinion, ZS Pharma is putting together the most robust and comprehensive clinical trial program for the treatment of both acute and chronic hyperkalemia.** As shown in exhibit 5, ZS Pharma has put together a comprehensive clinical program of over 1200 total patients tested to date and about 1500 total patients tested at the time of NDA submission in the first half of 2015. We believe the data presented at the analyst event further highlights the onset-of-action data and significant potential for ZS-9 to be a front-line therapy for hyperkalemia in the acute setting. In addition, the robust program allows for a comprehensive review of subgroups, which all suggest broad efficacy of ZS-9 and should ultimately allow for a broad product label. We also believe the comprehensive nature of the program should bode well if the company were to face an Advisory Committee alongside Relypsa's (RLPY $21.58) patiromer. We await the filing of the ZS-9 NDA, which management has guided to in the first half of 2015; however, there may be upside to this estimate as top-line data has been available since September for the company's second Phase III trial.

- We continue to rate shares of ZS Pharma Outperform with a price target of $75 given our belief that ZS-9 holds a best-in-class profile for the treatment of hyperkalemia. *In total, we believe the acute and chronic hyperkalemia market exceeds 3 million patients in the United States and has been reported in up to 10% of all hospitalized patients. In this large indication, there are few treatment options. Despite the recent concerns over edema observed in the HARMONIZE trial, we continue to believe that ZS-9 represents a significant advancement in the treatment of hyperkalemia over existing therapies and the competitive therapies in development.*

Additional Details:
In the first part of the event, CEO Robert Alexander gave an overview of the clinical program and market opportunity for ZS-9. In addition, he discussed preclinical toxicology studies, which had previously not been disseminated. To date, the company has completed both six-month rat and nine-month dog toxicology studies. Findings were related to hypokalemia at the highest dose tested (which was orders of magnitude higher than the dose taken in humans) and these findings were not present in potassium supplemented animals. In clinical studies, the company is also seeing dose-dependent decreases in serum aldosterone levels, which may have renal-protective effects. In mass balance studies to assess the absorption of the metal zirconium in ZS-9, recovery of zirconium in animal trials was similar to placebo and no studies showed any evidence of systemic absorption. Lastly, there was no measureable (parts per billion sensitivity) zirconium in dog urine in multidose toxicology studies as well as human urine from ZS004 patients.

The company still expects an NDA filing in the first half of 2015 with anticipated approval in the first half of 2016. Hyperkalemia affects approximately 4 million patients with CKD, diabetes, and heart failure in the United States, with both acute and chronic markets underserved. Current therapies include dietary restrictions on potassium rich foods, SPS/Kayexalate at 30-90 grams per day, diuretics, and medication avoidance or dose reduction (particularly of RAAS inhibitors).

The next speaker was the company's chief medical officer, Henrik Rasmussen, who gave an overview of the clinical program for ZS-9. To date, the company has patients on the drug out to eight months with about 1200 patients exposed to the drug to date. The company expects 1500 patients at the time of filing. In ZS002, patients were exposed to doses of 0.3 g, 3 g, and 10 g of ZS-9 with mean serum reduction in the 3 g and 10 g doses. The ZS002 adverse event (AE) profile included three AEs in placebo, one AE in the 0.3 g group, two AEs in the 3 g group, and eight AEs in 10 g group. Of the 10 g group, three (12.5%) patients presented with vomiting, two patients presented with UTIs (that upon further analysis were also present at baseline), and two patients with nausea (8.3%).

In the ZS003 study, patients were exposed to placebo, 1.25 g, 2.5 g, 5 g, or 10 g for a 48-hour induction phase and then a 12-day randomized withdrawal phase. At 48 hours, significant decreases in mean serum potassium levels were seen at the 2.5 g, 5 g, and 10 g doses. In addition, after completion of the study, a one-week withdrawal of ZS-9 treated patients showed that serum potassium increased back to placebo levels in patients when the drug was taken away. Lastly, the same levels of response occurred regardless of underlying etiologies (CKD, HF, with/without RAAS inhibitors, diabetes) with patients at higher baseline potassium levels brought down to normokalemic levels. In the ZS003 maintenance phase, the overall adverse event profile was similar between placebo and doses. Only one patient overall presented with hypokalemia, with no presence of UTIs, and edema levels not different between the doses tested and placebo. In addition, on further analysis, the researchers saw statistically significant improvements in bicarbonate levels, easing concerns about potential acidosis.

In the ZS004 study, the company had a 15 g dose group, primarily because it believes that the FDA likes to see higher doses and there was no indication at the 10 g dose of any adverse event issues in the previous studies. In addition, the company recruited patients with no upper limit on serum potassium due to the sharp decreases seen in ZS002 and ZS003 onset-of-action in bringing patients to a normokalemic level within 48 hours.

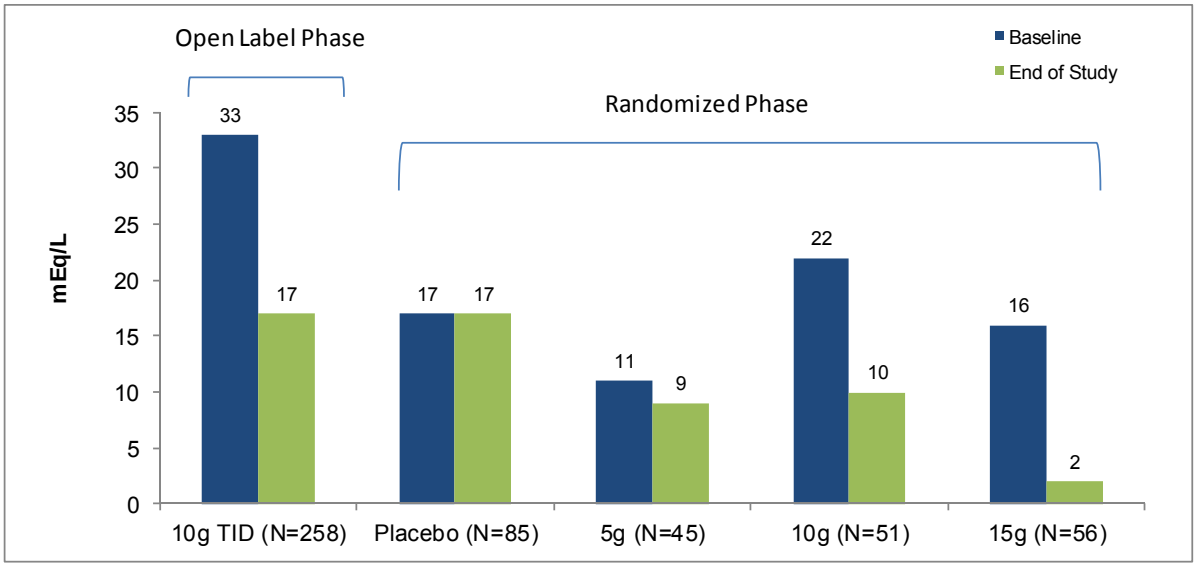
Lastly, Dr. Rasmussen gave an update on the ZS004 extension study, in which patients are entering the eighth month of dosing, and the ZS005 study that was initiated in the second half of 2014 and entering the sixth month.

Next, Dr. Kosiborod, the lead author of the *Journal of American Medical Association* paper and the presenter at AHA, spoke about the HARMONIZE results (which we detailed in our note on Tuesday, November 18) and further analysis of the edema subpopulation. Edema rates (defined as cases of edema divided by the number of patient days' exposure) were lower in the retrospective analysis of ZS003 with a placebo rate of 0.00011 and the ZS003 treatment groups (both 5 g and 10 g doses) of 0.00016. In the ZS004 extension study, the placebo rate was 0.00066; however, the 15 g dose exposure edema rate in the ZS004 extension study (1013 patient days) was 0.00000, lower than the placebo. The ZS005 open-label edema rate to date (6230 patient days) was 0.00016 with no patients currently titrated to the 15 g dose. In addition, 7 out of 14 patients did not require any treatment adjustment; of the patients with edema, 7 out of 8 had peripheral edema (with the majority being foot/ankle edema). We believe that the edema rate seen in the HARMONIZE results were due to an artifact seen as a result of randomization in the study where patients in the 15 g dose included patients with a lower glomerular filtration rate (patients farther along in chronic kidney disease) and increased brain natriuretic peptide (a marker for increased chronic cardiovascular disease). Dr. Kosiborod hypothesized that the results were likely a chance finding, since ZS003 and the extension studies to date have seen no effects. He also highlighted that these results could be a paradigm shift in hyperkalemia management in both acute and chronic settings.

The last speaker was Dr. Frank Peacock, an emergency room physician, who highlighted the impact that ZS-9 could have in the acute setting. According to Dr. Peacock's presentation, 700,000 hospital admissions in 2006 were due to hyperkalemia, with severe hyperkalemia (greater than or equal to 5.8 mEq.L) often requiring treatment in the ER. In addition, there was 6 times the rate of one-day mortality in patients with potassium greater than 5.5 versus less than 5.5, and a 3.7% mortality rate within one day of a hyperkalemic event above 6 mEq/L. Dr. Peacock then detailed the inadequacy of current acute therapies to provide a longer-term effect,with calcium onset lasting 30-60 minutes, alkalination lasting 15-30 minutes, glucose/insulin effective for 1-2 hours, beta-adrenergic agonists being effective for only 2 hours, loop diuretics only being effective for 20-60 minutes and not working in end-stage renal patients, and binding resins having an onset of action of 2 to 12 hours. In addition, most patients refuse to take binding resins due to diarrhea/constipation.

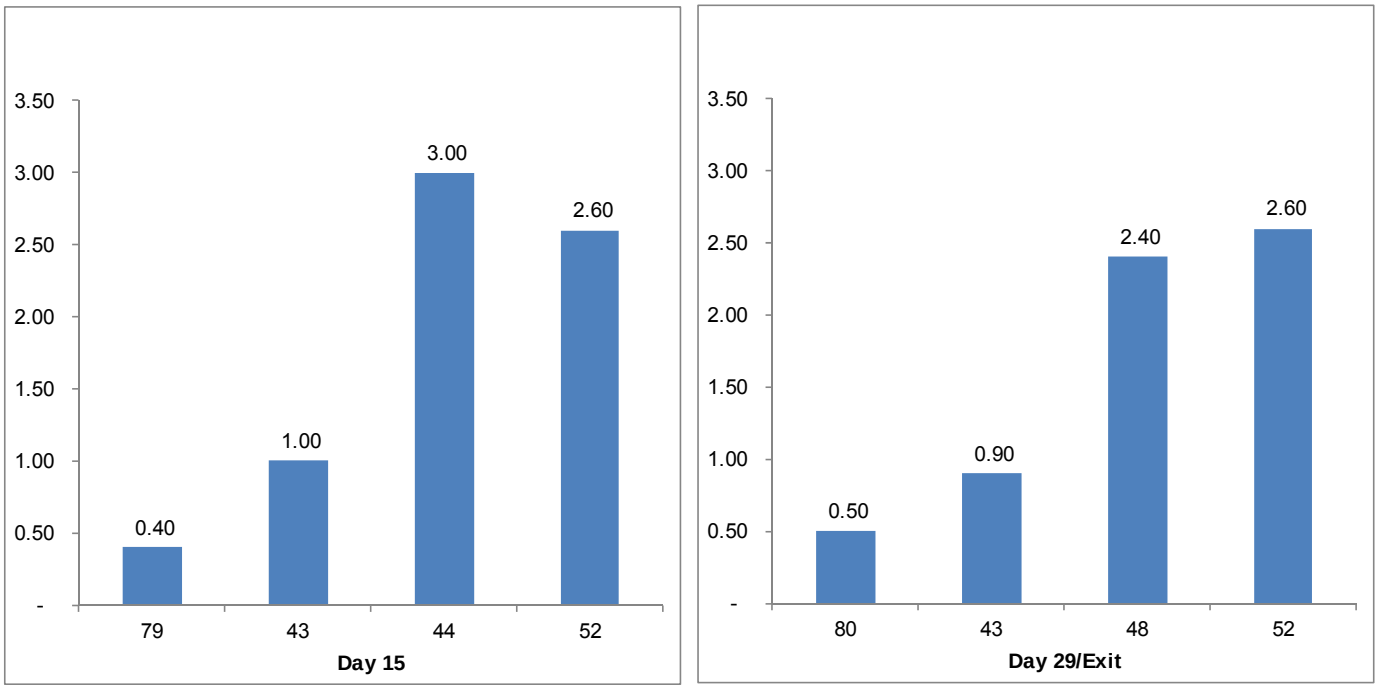
With a small retrospective look at patients with potassium greater than 6 mEq/L, a single 10 g dose lowered potassium by an average of 0.5 in 1 hour, 0.7 in 2 hours, and 1 in 24 hours. Median time to below 6 mEq/L was 1.05 hours and median time to less than 5.5 mEq was 4 hours. We believe this onset of action could be a key differentiator with other therapies that are in the market as well as those in development.

Exhibit 1
ZS Pharma
Proporation of Patients with Low Bicarbonate



Source: ZS Analyst Event

Exhibit 2
Bicarbonate Change from Baseline (bicarbonate mEq/L)



Source: ZS Pharma Analyst Event

Exhibit 3
Edema Rates Over ZS-9 Clinical Program

Study	Edema Rate
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*
ZS004 15g dose (exposure: 1,013 patient days)	*0.000000*
ZS005 Open-Label Study (5, 10, 15g*) - Ongoing (exposure: 6,230 patient days)	0.00016

Source: ZS Pharma Analyst Event

*No one titrated to 15g

Exhibit 4
ZS Pharma, Inc.
Patient Baseline Characteristics in HARMONIZE Study

	Open-Label	Randomized Phase							
	10 g (n=258)	Placebo (N=85)	5g (N=45)	vs. Placebo	10g (N=51)	vs. Placebo	15g (N=56)	vs. Placebo	Comments
Median Age (years)	65	66	64	-2	65	-1	65	-1	
Male %	58	52	60	8	53	1	71	19	
White %	83	86	80	-6	86	0	82	-4	
Black %	14	12	18	6	10	-2	16	4	
Baseline Serum K+ <5.5 mEq/L %	46	51	51	0	37	-14	43	-8	
Baseline Serum K+ 5.5-<6.0 mEq/L %	39	35	38	3	45	10	46	11	
Baseline Serum K+ ≥ 6.0 mEq/L %	15	14	11	-3	18	4	11	-3	
RAAS inhibitors %	70	72	73	1	71	-1	59	-13	Less RAAS inhibitor use in 15g pts
Heart Failure %	36	31	40	9	35	4	45	14	8 more pts with heart failure in 15g group
Diabetes Mellitus %	66	64	58	-6	75	11	70	6	More diabetics in 10g and 15g groups
Baseline eGFR <60 %	69	61	69	8	75	14	73	12	12% more CKD pts in 15g group vs. placebo in 15g dose
Brain Natriuretic Peptide (pg/mL)	126	101	175	74	101	0	152	51	50% higher BNP vs. placebo in 15g dose

Source: American Heart Association 2014 Annual Meeting

Exhibit 5
ZS Phama, Inc.
ZS-9 Development Program Overview

Trial	Patient Population	Duration	Objective	Summary
ZS002 (Completed)	N=90 Hyperkalemia, CKD 5-6 mEq/L	48 hours	POC for ZS-9 rapidly lowering K+ levels	Met primary endpoint
ZS003 (Completed)	N=753 Hyperkalemia, regardless of etiology. 5-6 mEq/L	14 days	Confirm rapid K+ control and POC for extended dosing	Met primary endpoint for the 2.5, 5, 10 doses and secondary endpoints for 5 and 10 dose in extended phase
ZS004/e (Completed/Ongoing)	N=258 Hyperkalemia, regardless of etiology. >5 mEq/L	1 month + 11 month extension	Establish an extended dose	80%, 90%, and 94% normokalemic at 5g, 10g, and 15g QD doses, respectively
ZS005 (Ongoing)	N=500 Hyperkalemia, regardless of etiology. >5 mEq/L	12 months	Establishing long-term safety and efficacy	Initated 2Q14

Source: ZS Pharma reports

Valuation

We rate shares of ZS-9 Outperform with a $75 price target. Our price target is derived from our net-present-value model for ZS-9 and applying a 75% probability of success. Swing factors in our peak-year estimates include patient duration, which we estimate will reach six months; however, if ZS Pharma is successful in penetrating the chronic therapy market, this duration might hold upside. Currently, we anticipate peak sales for ZS-9 of $1.17 billion by penetrating 10% to 13% of the available patient populations within select markets.

Risks

Risks to an investment in ZS Pharma include the normal clinical, regulatory, and commercial risks in development-stage therapeutics companies.

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William Blair was a manager or co-manager of a public offering of equity securities for ZS Pharma, Inc. within the prior 12 months.

William Blair is a market maker in the security of ZS Pharma, Inc. and may have a long or short position.

William Blair intends to seek investment banking compensation in the next three months from ZS Pharma, Inc.

Within the past 12 months William Blair has provided or is providing investment banking services to or has an investment services relationship with ZS Pharma, Inc.

Additional information is available upon request.

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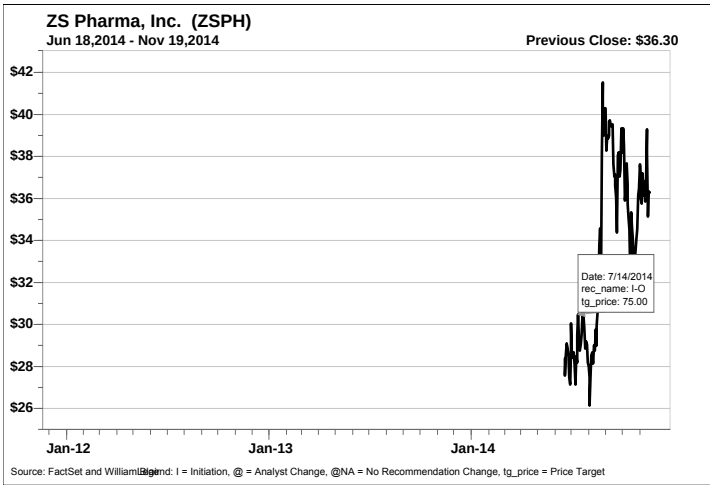
DOW JONES: 17,685.73
S&P 500: 2,048.72
NASDAQ: 4,675.71



Current Rating Distribution (as of 10/31/14)

Coverage Universe	Percent	Inv. Banking Relationships*	Percent
Outperform (Buy)	65	Outperform (Buy)	16
Market Perform (Hold)	31	Market Perform (Hold)	3
Underperform (Sell)	1	Underperform (Sell)	0

*Percentage of companies in each rating category that are investment banking clients, defined as companies for which William Blair has received compensation for investment banking services within the past 12 months.

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