William Blair

ZS Pharma, Inc.

November 18, 2014

HARMONIZE Presented at AHA and Published in JAMA, Edema Risk Overblown, Buy on Weakness

- Monday morning, November 17, ZS Pharma presented at the Annual Meeting of the American Heart Association in Chicago the full data set from its second pivotal Phase III study entitled HARMONIZE. This presentation was highly anticipated after the company announced in September positive top-line data with a statistically significant top-line result in all three doses of ZS-9 in the reduction of serum potassium levels in patients with hyperkalemia. As shown in exhibits 1 and 2, on page 3, the primary endpoint of the study, mean potassium levels on maintenance therapy (days 8-29), was statistically significant in 5 gram, 10 gram, and 15 gram dose groups, with 46% of patients reaching normal potassium levels in the placebo group, while 80%, 90%, and 94% reached normal levels in the respective 5 gram, 10 gram, and 15 gram groups. In addition, the efficacy was consistent in all subgroups, which included patients with chronic kidney disease, heart failure, diabetes mellitus, and on RAAS inhibitors.

- We believe the data set shows a clear efficacy profile; however, we believe concerns over adverse events in the 15 gram arm likely led to Monday's share weakness, which we view as a buying opportunity as ZS-9 continues to look like the best-in-class therapy. While the gastrointestinal adverse events were 14% in the placebo group, and lower in each of the ZS-9 treated groups (5 g: 7%, 10 g 2%, 15 g: 9%) the concern from investors likely lies in the higher rates of edema in the 15 g dose. Overall edema occurred in two (2%) placebo patients, one (2%) patient in the 5 gram arm, three (6%) in the 10 gram arm, and eight (14%) in the 15 gram arm. Of the patients with edema, 50% did not require treatment while 13 out of the 14 patients with edema finished the study and had only peripheral edema. Based on our discussions, management believes the increase in edema is study-related artifact; we highlight in exhibit 5 the baseline statistics of the treatment groups, specifically showing that the 15 gram patients were in worse health than placebo patients. We also believe yet to be published data from the ZS004 open label extension study—where patients are treated with 10 grams per day, once-a-day, and titrated up or down depending on need—also reaffirms the clean safety profile of ZS-9. Management believes patients to date in the extension portion of ZS004 when corrected for exposure (given the long-term nature of the study) have a lower edema rate than the two patients with edema in the placebo group over 28 days. We note that there were no urinary tract infections in the HARMONIZE study, a concern much like the current concern with edema, which was raised earlier in the development of ZS-9.

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

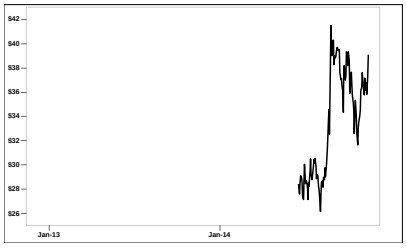
Stock Rating:	**Outperform**
Company Profile:	**Aggressive Growth**
Price Target:	$75.00
Symbol:	ZSPH (NASDAQ)
Price:	$35.14 (52-Wk.: $26-$43)
Market Value (mil.):	$732
Fiscal Year End:	December
Long-Term EPS Growth Rate:	
Dividend/Yield:	None

	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	139,625

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

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

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

Please consult pages 8-9 of this report for all disclosures. Analyst certification is on page 8.
William Blair & Company, L.L.C. does and seeks to do business with companies covered in its research reports. As a result, investors should be aware that the firm may have a conflict of interest that could affect the objectivity of this report. Investors should consider this report as a single factor in making an investment decision.

- Other questions raised by discussants and audience members also included potential issues that may arise from patients on metformin, given the guanidine containing compound and risk of acidosis. With 66% of patients from HARMONIZE diabetic, and urinary pH levels all suggesting no acidotic conditions, we do not believe metformin use in combination with ZS-9 is a risk. We actually believe pH levels on average have increased in treated patients in all studies to date. Management also assured us that the data from animal toxicity studies as well as the open-label extension studies have shown no increases in edema after treatment. With an over 500-patient long-term safety study ongoing with data over seven months, we believe the data to be released in 2015 will be the ultimate answer for safety questions in investor minds. Outside of the questions regarding edema, we continue to believe that the lower gastrointestinal adverse events observed with ZS-9 to date may be attributed to the smaller volume of the zirconium silicate crystalline form that does not induce swelling in the patient's GI tract, which continues to be a differentiating factor from patiromer. In HARMONIZE constipation rates were higher in placebo (7.1%) than 5 grams (0%), 10 grams (2%), and 15 grams (1.8%). Lastly, there were no changes in serum ions of sodium, magnesium, and calcium, as well as no increases in urinary sodium excretion. In fact, there were dose-dependent increases in bicarbonate levels, which rule out the potential for acidosis that was a concern in the diabetic population.

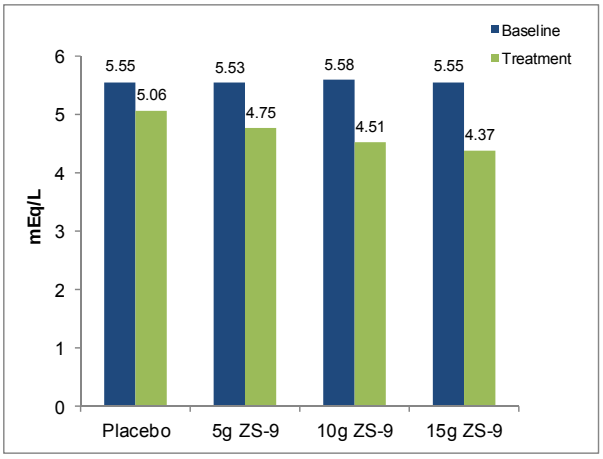
- The company is hosting an analyst event on November 19 in New York City, and we expect the company to further address concerns over edema and urinary pH and highlight the consistent efficacy observed from ZS-9 to date. We also believe the company will highlight animal and clinical data suggesting that ZS-9 is indeed a GI localized therapy with no difference in zirconium levels between placebo and active patients. Case studies for the edema patients will also likely be highlighted with management describing an example of one edema patient as a male, 64 years old, with a history of edema prior to entering the study as well as CKD and diabetes.

- While safety was clearly the focus of investors, efficacy continues to look impressive after we believe patiromer onset of action results disappointed at last week's ASN Kidney Week. In the 48 hour open-label induction phase of HARMONIZE, patients with mean baseline serum potassium of 5.55 mEq/L saw a median time to K+ normalization in 2.2 hours, 84% of patients normalized by 24 hours, and 98% of patients normalized by 48 hours. These results were consistent with ZS003 induction phase results with 99% of patients being normokalemic within 48 hours. In addition, in the HARMONIZE study, patients achieved normokalemia regardless of the baseline serum potassium levels with a 0.8 mEq/L decrease in patients with baseline <5.5 mEq/L and a 1.5 mEq/L decrease in patients with baseline ≥6.0 mEq/L.

- The HARMONIZE study was a randomized, double-blind, placebo-controlled trial in ambulatory patients with prior history or laboratory evidence of hyperkalemia being recruited from 44 nephrology, cardiology, or general research sites of which 80% were in the United States, 12% in South Africa, and 8% in Australia. Inclusion criteria were potassium values greater than or equal to 5.1 mEq/L with no upper limit at entry and the ability to have repeated blood draws. Exclusion criteria included dialysis requirement, cardiac arrhythmias requiring immediate treatment, active therapy with SPS/Kayexalate, life expectancy less than three months, and pregnancy.

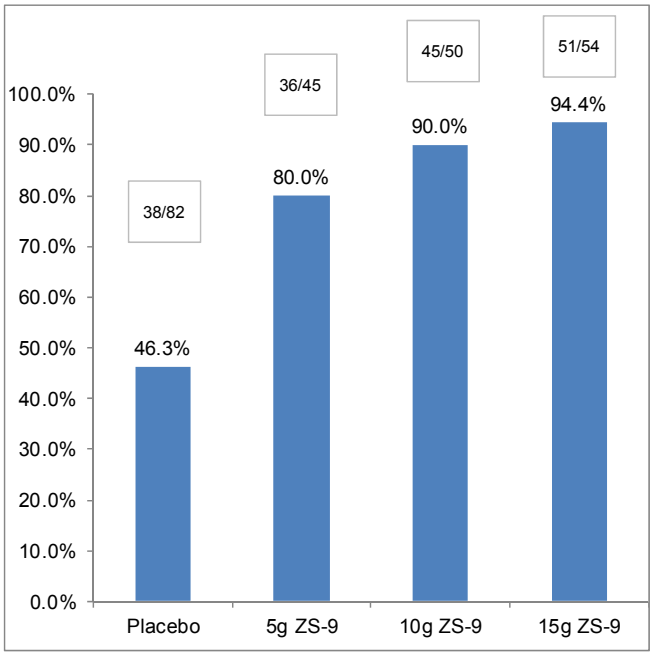
- We continue to rate shares of ZS Pharma Outperform with a price target of $75 given our belief that ZS-9 holds a best-in-class profile for the treatment of the large hyperkalemia market. *In total, we believe the hyperkalemia market exceeds 3 million patients in the United States and has been reported in up to 10% of all hospitalized patients. We also believe there are few good treatment options for patients with hyperkalemia and despite concerns over the edema in HARMONIZE, we continue to believe ZS-9 holds a best-in-class profile.*

Exhibit 1
ZS Pharma
HARMONIZE Primary Endpoint: Mean K+ Maintenance on Days 8-29



Source: American Heart Association Annual Meeting 2014

Exhibit 2
% of Total Patients with Mean Potassium <5.1 mEq/L, days 8-29



Source: Kosiborod et al. *JAMA* 2014

Exhibit 3
Secondary Endpoints

Endpoint	Placebo	5g ZS-9 (N=45)	P value	10g ZS-9 (N=50)	P value	15g ZS-9 (N-54)	P value
Proportion of normokalemic patients							
Day 15	43.8%	70.5%	0.005	85.1%	<.001	82.7%	<.001
Day 29	47.6%	71.1%	0.010	76.0%	0.002	85.2%	<.001
Mean change in potassium from open-label phase at baseline							
Day 15	-8.3%	-13.7%	0.004	-19.3%	<.001	-21.2%	<.001
Day 29	-7.7%	-13.9%	<.001	-19.3%	<.001	-21.1%	<.001
Mean change in potassium from randomized phase baseline							
Day 15	12.5%	6.0%	0.020	2.9%	<.001	-1.9%	<.001
Day 29	13.0%	6.1%	0.008	3.0%	<.001	-1.4%	<.001
Time to first hyperkalemic measure, median in days	7	14	0.002	28	<.001	NR	<.001
Time to first return to open-label phase baseline, median in days	19	29	0.006	NR	<.001	NR	<.001
Mean intra-participant potassium SD during randomized phase	0.06	0.06	0.960	0.08	0.008	0.07	0.340
Mean change in serum aldosterone							
Day 29	-0.8	-4.8	0.010	-6.1	0.010	-3.7	0.020
Mean change in plasma renin							
Day 29	3	0.8	0.330	-2.3	0.030	-0.32	0.230
Days with normokalemia (mean #/total #, range)	7.4/22	13.4/22 (11.1 to 15.6)	<.001	13.9/22 (11.6 to 16.1)	<.001	16.8/22 (14.9 to 18.7)	<.001

Source: Kosiborod et al. *JAMA* 2014

Exhibit 4

HARMONIZE Adverse Events and Serious Adverse Events**

Adverse Events	Open Label Phase (ZS-9 10g, N=258)	Placebo (N=85)	5g ZS-9 (N=45)	10g ZS-9 (N=51)	15g ZS-9 (N=56)
Any Event	20 (7.8%)	27 (31.8%)	24 (53.3%)	15 (29.4%)	25 (44.6%)
Anemia	0	0	0	0	3 (5.4%)
Constipation	2 (0.8%)	6 (7.1%)	0	1 (2.0%)	1 (1.8%)
Edema	0	2 (2.4%)	1 (2.2%)	3 (5.9%)	8 (14.3%)
Hypokalemia (all)	0	0	0	5 (9.8%)	6 (10.7%)
Hypokalemia (reported as AE)	0	0	0	0	1 (1.8%)
Nasopharyngitis	0	1 (1.2%)	0	0	3 (5.4%)
Upper respiratory tract infection	1 (0.4%)	1 (1.2%)	3 (6.7%)	1 (2.0%)	1 (1.8%)

Serious Adverse Events*	Open Label Phase (ZS-9 10g, N=258)	Placebo (N=85)	5g ZS-9 (N=45)	10g ZS-9 (N=51)	15g ZS-9 (N=56)
Any event	0	0	5 (11.1%)	2 (3.9%)	3 (5.4%)
Cardiac failure, congestive	0	0	1 (2.2%)	0	0
Myocardial infarction	0	0	0	1 (2.0%)	0
Small intestinal obstruction	0	0	1 (2.2%)	0	0
Generalized edema	0	0	0	0	1 (1.8%)
Hepatotoxicity	0	0	1 (2.2%)	0	0
Cellulities	0	0	0	1 (2.0%)	0
Pneumonia	0	0	1 (2.2%)	0	1 (1.8%)
Confusional state	0	0	1 (2.2%)	0	0
Dyspnea	0	0	0	0	1 (1.8%)

*None of the serious adverse events were deemed by the investigator to be related to study treatment

**Adverse Events Occurring in 5% or More of Patients in Any Group and All Serious Adverse Events

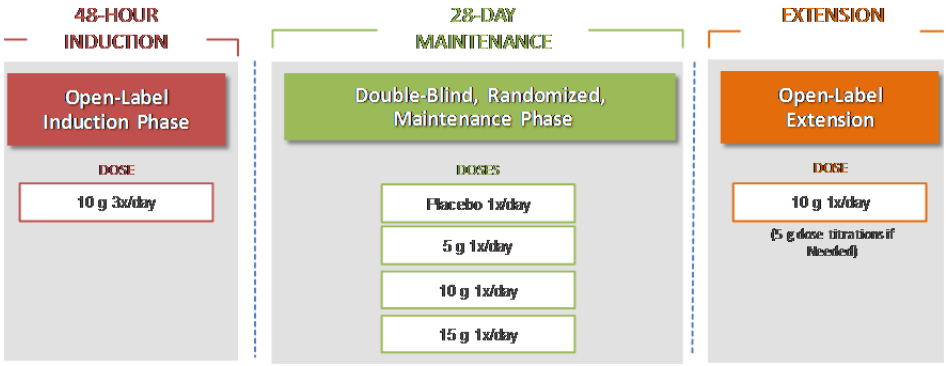
Source: Kosiborod et al. *JAMA* 2014

Exhibit 5
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 6
ZS Pharma, Inc.
HARMONIZE Study Design



Primary Endpoint: Comparison of mean serum K^+ levels from day 8 to day 28

Secondary Endpoints: Proportion of patients normokalemic after induction phase
Proportion of patients normokalemic during 28-day maintenance period

Source: Company reports

IMPORTANT DISCLOSURES

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.

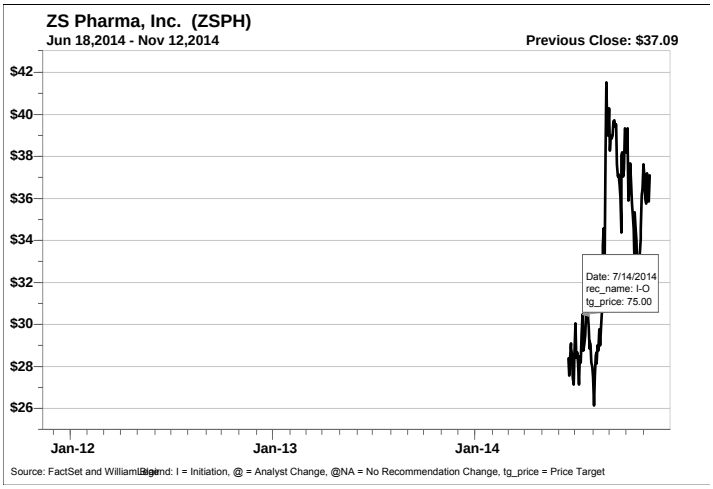
Additional information is available upon request.

This report is available in electronic form to registered users via R*Docs™ at www.rdocs.com or www.williamblair.com.

Please contact us at +1 800 621 0687 or consult williamblair.com/Research-and-Insights/Equity-Research/Coverage.aspx for all disclosures.

Tim Lugo attests that 1) all of the views expressed in this research report accurately reflect his/her personal views about any and all of the securities and companies covered by this report, and 2) no part of his/her compensation was, is, or will be related, directly or indirectly, to the specific recommendations or views expressed by him/her in this report. We seek to update our research as appropriate, but various regulations may prohibit us from doing so. Other than certain periodical industry reports, the majority of reports are published at irregular intervals as deemed appropriate by the analyst.

DOW JONES: 17,647.75
S&P 500: 2,041.32
NASDAQ: 4,671.00



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.

The compensation of the research analyst is based on a variety of factors, including performance of his or her stock recommendations; contributions to all of the firm's departments, including asset management, corporate finance, institutional sales, and retail brokerage; firm profitability; and competitive factors.

OTHER IMPORTANT DISCLOSURES

Stock ratings, price targets, and valuation methodologies: William Blair & Company, L.L.C. uses a three-point system to rate stocks. Individual ratings and price targets (where used) reflect the expected performance of the stock relative to the broader market (generally the S&P 500, unless otherwise indicated) over the next 12 months. The assessment of expected performance is a function of near-, intermediate-, and long-term company fundamentals, industry outlook, confidence in earnings estimates, valuation (and our valuation methodology), and other factors. Outperform (O) – stock expected to outperform the broader market over the next 12 months; Market Perform (M) – stock expected to perform approximately in line with the broader market over the next 12 months; Underperform (U) – stock expected to underperform the broader market over the next 12 months; not rated (NR) – the stock is not currently rated. The valuation methodologies used to determine price targets (where used) include (but are not limited to) price-to-earnings multiple (P/E), relative P/E (compared with the relevant market), P/E-to-growth-rate (PEG) ratio, market capitalization/revenue multiple, enterprise value/EBITDA ratio, discounted cash flow, and others.

Company Profile: The William Blair research philosophy is focused on quality growth companies. Growth companies by their nature tend to be more volatile than the overall stock market. Company profile is a fundamental assessment, over a longer-term horizon, of the business risk of the company relative to the broader William Blair universe. Factors assessed include: 1) durability and strength of franchise (management strength and track record, market leadership, distinctive capabilities); 2) financial profile (earnings growth rate/consistency, cash flow generation, return on investment, balance sheet, accounting); 3) other factors such as sector or industry conditions, economic environment, confidence in long-term growth prospects, etc. Established Growth (E) – Fundamental risk is lower relative to the broader William Blair universe; Core Growth (C) – Fundamental risk is approximately in line with the broader William Blair universe; Aggressive Growth (A) – Fundamental risk is higher relative to the broader William Blair universe.

The ratings, price targets (where used), valuation methodologies, and company profile assessments reflect the opinion of the individual analyst and are subject to change at any time.

Our salespeople, traders, and other professionals may provide oral or written market commentary or trading strategies—to our clients and our trading desks—that are contrary to opinions expressed in this research. Certain outstanding reports may contain discussions or investment opinions relating to securities, financial instruments and/or issuers that are no longer current. Always refer to the most recent report on a company or issuer before making an investment decision. Our asset management and trading desks may make investment decisions that are inconsistent with recommendations or views expressed in this report. We will from time to time have long or short positions in, act as principal in, and buy or sell the securities referred to in this report. Our research is disseminated primarily electronically, and in some instances in printed form. Electronic research is simultaneously available to all clients. This research is for our clients only. No part of this material may be copied or duplicated in any form by any means or redistributed without the prior written consent of William Blair & Company, L.L.C.

THIS IS NOT IN ANY SENSE A SOLICITATION OR OFFER OF THE PURCHASE OR SALE OF SECURITIES. THE FACTUAL STATEMENTS HEREIN HAVE BEEN TAKEN FROM SOURCES WE BELIEVE TO BE RELIABLE, BUT SUCH STATEMENTS ARE MADE WITHOUT ANY REPRESENTATION AS TO ACCURACY OR COMPLETENESS OR OTHERWISE. OPINIONS EXPRESSED ARE OUR OWN UNLESS OTHERWISE STATED. PRICES SHOWN ARE APPROXIMATE.

THIS MATERIAL HAS BEEN APPROVED FOR DISTRIBUTION IN THE UNITED KINGDOM BY WILLIAM BLAIR INTERNATIONAL, LIMITED, REGULATED BY THE FINANCIAL CONDUCT AUTHORITY (FCA), AND IS DIRECTED ONLY AT, AND IS ONLY MADE AVAILABLE TO, PERSONS FALLING WITHIN COB 3.5 AND 3.6 OF THE FCA HANDBOOK (BEING "ELIGIBLE COUNTERPARTIES" AND "PROFESSIONAL CLIENTS"). THIS DOCUMENT IS NOT TO BE DISTRIBUTED OR PASSED ON TO ANY "RETAIL CLIENTS." NO PERSONS OTHER THAN PERSONS TO WHOM THIS DOCUMENT IS DIRECTED SHOULD RELY ON IT OR ITS CONTENTS OR USE IT AS THE BASIS TO MAKE AN INVESTMENT DECISION.

"William Blair" and "R*Docs" are registered trademarks of William Blair & Company, L.L.C. Copyright 2014, William Blair & Company, L.L.C. All rights reserved.