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ZS Pharma, Inc.

NKF Clinical Meeting Kicks Off Hyperkalemia Physician Education, Differences in Pipeline Therapies Are Refined

- We recently attended the National Kidney Foundation's Spring Clinical Meeting in Dallas to get a first glimpse at what we expect will be an ongoing theme in 2015 for ZS Pharma and Relypsa (RLYP $34.11), the education of clinicians on the unmet medical need in hyperkalemia (increased serum potassium that has been shown to be associated with increased cardiovascular events and mortality), the lack of adequate approved therapies for both acute and chronic treatment, and the value proposition for both companies' lead products to treat hyperkalemia.

- In one of several symposiums on hyperkalemia, Dr. Wolfgang Winkelmayer presented an overview of clinical trials with ZS-9 and patiromer from recently published articles in the *New England Journal of Medicine* and the *Journal of the American Medical Association*. In exhibit 1, on page 3, we highlight some characteristics of the patients enrolled in each of the three studies. In the Weir et al. publication, patients were enrolled in the trial if they met the criteria of being in stage 4/5 of chronic kidney disease and if they had been on RAAS inhibitor therapy for over four weeks. In the ZS-9 trials, patients were enrolled regardless of their CKD state and RAAS inhibitor therapy (although approximately two-thirds of patients were on RAAS inhibitors). After speaking with some physicians at the meeting, we believe that in the regulatory review process, patiromer could receive a label that includes only patients on RAAS inhibitor therapy and more developed CKD as opposed to ZS-9, which has been shown to be effective in maintaining normokalemia in a more heterogeneous population; this may serve as a differentiator with both potentially in the market by the end of 2016.

- Also noted by physicians we spoke with at the conference, all of the patients in the Weir et al. study were Caucasian (as we have discussed in other notes, a significant population of study sites were in Eastern Europe), whereas the ZS-9 trials had recruited patients of other descent (about 20%) with a majority of trial sites in the United States in much larger studies. As shown in exhibit 2, on page 3, there have been several published studies showing the racial disparities in kidney disease outcomes skewed toward U.S. minorities in having a greater risk of developing more severe CKD. We believe this could be an issue upon regulatory review for patiromer's FDA approval with an increasing awareness of the under-representation of racial minorities in clinical trials versus "the patient population to which drug use will be generalizable upon approval" (Wissing et al. *Cancer* 2014).

Stock Rating:	**Outperform**
Company Profile:	**Aggressive Growth**
Price Target:	$75.00
Symbol:	ZSPH (NASDAQ)
Price:	$40.93 (52-Wk.: $26-$53)
Market Value (mil.):	$1,020
Fiscal Year End:	December
Long-Term EPS Growth Rate:	
Dividend/Yield:	None

	2014A	2015E	2016E
Estimates			
EPS FY	$-5.47	$-3.90	$-3.84
CY		$-3.90	$-3.84
Sales (mil.)	0	0	37
Valuation			
FY P/E	NM	NM	NM
CY P/E		NM	NM

Trading Data (FactSet)	
Shares Outstanding (mil.)	21
Float (mil.)	20
Average Daily Volume	245,104

Financial Data (FactSet)	
Long-Term Debt/Total Capital (MRQ)	0.1
Book Value Per Share (MRQ)	4.6
Return on Equity (TTM)	-124.1

Two-Year Price Performance Chart

Sources: FactSet, William Blair & Company estimates

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

- In another symposium on hyperkalemia, Dr. Peter McCullough presented an overview of both ZS-9 and patiromer. In regard to their chemical composition, Dr. McCullough gave a brief history of each compound, with patiromer having the ability to bind calcium and magnesium but a primary site of action in the colon. For ZS-9, he described the compound's ability to bind ammonia, the zirconium silicate base (which he also said was a non-issue), and the site of action upstream of the colon. He mentioned that patiromer was titrated in its published clinical trials versus set dosing for ZS-9. In addition, he cited that ZS-9 had a faster onset of action in clinical trials versus patiromer; however, he also noted that neither drug has been applied in the emergency room setting in clinical trials to date. Overall, most physicians we spoke with at the conference believe that both drugs will be successful in the U.S. and E.U. regulatory processes, but were concerned about pricing of the drugs with the potential for long-term therapy in chronic hyperkalemia cases that manifest in the majority of late-stage chronic kidney disease patients.

- Both companies also presented subgroup analyses of their recent pivotal clinical trials (Relypsa: OPAL-HK, ZS Pharma: HARMONIZE) in patients with Stage 4/5 CKD (84 patients with eGFR <30mL/min/1.73m^2 in HARMONIZE and 109 patients with a mean of 21.3 mL/min/1.73m^2 ± 5.4 30mL/min/1.73m^2 in OPAL-HK). In both studies, patients had clinically meaningful decreases in serum potassium by the end of the study. However, in line with what was viewed in the larger patient populations, ZS-9 had a much faster onset of action compared with patiromer, with a 1.2 mEq/L reduction (about 5.7 mEq/L to about 4.5 mEq/L) at 48 hours in HARMONIZE versus an approximately 0.4 m/Eq/L reduction (about 5.6 mEq/L to about 5.2 mEq/L) at day 3 in OPAL-HK. ZS Pharma also presented several posters at the conference outside the symposiums. Of note was the analysis of GI adverse effects in HARMONIZE, which actually showed lower rates of GI disorders versus the placebo group (exhibit 3, on page 4). This is important because the majority of physicians we spoke with stated that a major issue with Kayexalate (the current standard-of-care) was the significant GI adverse effects.

- Given the recent Neupogen biosimilar FDA approval as well as the proof-of-concept implementation in the European Union, we note that the other major theme we noticed at the conference was the physician education symposiums on biosimilars. We believe biosimilars are going to continue to be a theme in the future as the 351(k) pathway continues to be refined to provide a similar pricing pressure that generics applied to branded small molecule drugs with the Hatch-Waxman Act. The case for biosimilars in the United States was strengthened by their relative success in Europe. There are currently 19 biosimilars approved for use by the EMA, with Somatropin approval being the first in April 2006. In exhibit 4, on page 4, we show several biologics that have expired (or upcoming expirations of) patents in the United States that will entice companies to continue to develop and commercialize biosimilars. As biosimilars will likely have a role in the chronic kidney disease setting, companies facing pressure on these legacy franchise or those looking to enter the market with a brand biosimilar strategy may be attractive strategic partners for the marketers of hyperkalemia therapies.

- 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 with few good treatment options. While we believe the market may be large enough for two winners, we ultimately view the profile of ZS-9 as the likely best-in-class product and we believe long-term safety data, which should be available later in the year at an appropriate medical meeting, will likely cement that profile. The next meaningful catalysts for ZS Pharma will likely be the filing of the ZS-9 NDA and long-term safety study data (exhibit 5, on page 5), which we believe may occur in the near term. We continue to view ZS Pharma as a top idea in 2015.*

Valuation

We rate shares of ZS Pharma 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.

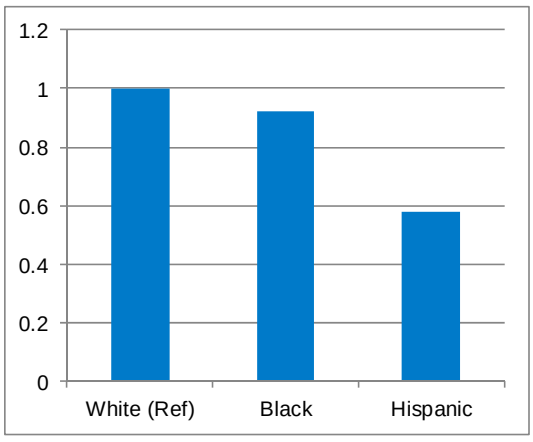
Exhibit 1
Selected Baseline Characteristics for Published Hyperkalemia Studies with ZS-9 and Patiromer

Characteristic	Weir et al. NEJM 2015	Kosiborod et al. JAMA 2014	Packham et al. NEJM 2015
N	Treatment Phase (N=243), Randomized Withdrawal Phase (Placebo N=52, Patiromer N=55)	Open-Label Phase (N=258), Randomized Phase (Placebo N=85, 5g ZS-9: N=45, 10g ZS-9 N=51, 15g ZS-9 N-56)	Placebo N=158, 1.25g ZS-9: N=154, 2.5g ZS-9 N=141, 5g ZS-9 N=157, 10g ZS-9 N=143
RAAS inhibitor use	Initial Treatment Phase: 100%; Randomized Withdrawal Phase: Placebo 100%, Patiromer 100%	Open-Label Phase: 69.8%, Randomized Phase: Placebo 71.8%, 5g ZS-9 73.3%, 10g ZS-9 70.6%, 15g ZS-9 58.9%	Placebo 63.9%, 1.25g ZS-9: 70.8%, 2.5g ZS-9 68.8%, 5g ZS-9 63.1%, 10g ZS-9 67.1%
eGFR: mean (SD)	Treatment Phase: 35.4 (16.2), Randomized Withdrawal Phase: Placebo 39 (20.4), Patiromer 38.6 (20.7)	Open-Label Phase: 46.3 (30.5), Randomized Phase: Placebo 48 (28.8), 5g ZS-9 48 (30.7), 10g ZS-9 44.7 (30.7), 15g ZS-9 44.9 (29.5)	Not reported, no specific requirements for GFR nor were patients excluded on the basiis of date of initiation of RAAS inhibitor
Caucasian ('White race')	Initial Treatment Phase 98%, Randomized Withdrawal 100%	Open-Label Phase: 83.3%, Randomized Phase: Placebo 85.9%, 5g ZS-9 80%, 10g ZS-9 86.3%, 15g ZS-9 82.1%	Placebo 86.1%, 1.25g ZS-9: 85.1%, 2.5g ZS-9 88.7%, 5g ZS-9 84.1%, 10g ZS-9 83.9%
Black/African American	Not reported	Open-Label Phase: 14.3%, Randomized Phase: Placebo 11.8%, 5g ZS-9 17.8%, 10g ZS-9 9.8%, 15g ZS-9 16.1%	Placebo 10.8%, 1.25g ZS-9: 13%, 2.5g ZS-9 7.8%, 5g ZS-9 12.7%, 10g ZS-9 13.3%
Asian	Not reported	Open-Label Phase: 1.9%, Randomized Phase: Placebo 3.5%, 5g ZS-9 0%, 10g ZS-9 2%, 15g ZS-9 1.8%	Not reported
Other	Not reported	Open-Label Phase: 1.2%, Randomized Phase: Placebo 1.2%, 5g ZS-9 2.2%, 10g ZS-9 2%, 15g ZS-9 0%	Not reported

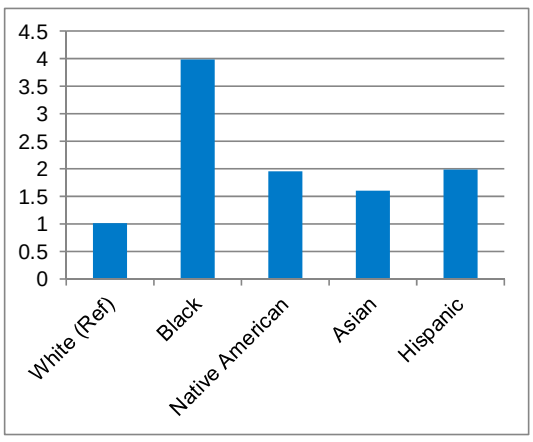
Sources: Weir et al. NEJM 2015, Kosiborod et al. JAMA 2014, Packham et al. NEJM 2015

Exhibit 2
Prevalence of CKD By Race

Relative Prevalence of Stage 1-3 CKD



Relative Prevalence of ESRD



Sources: Nicholas SB et al. Sem in Nephrol 2013

Exhibit 3
GI Adverse Effects in Maintenance Phase of HARMONIZE

	Maintenance Phase			
Adverse Event	Placebo (N=85)	5g (N=45)	10g (N=51)	15g (N=56)
GI disorders, overall	12 (14.1%)	3 (6.7%)	1 (2.0%)	5 (8.9%)
Abdominal pain	1 (1.2%)	1 (2.2%)	0	0
Constipation	6 (7.1%)	0	1 (2.0%)	1 (1.8%)
Diarrhea	1 (1.2%)	0	0	2 (3.6%)
Dyspepsia	0	2 (4.4%)	0	0
Nausea	1 (1.2%)	0	0	1 (1.8%)
Vomiting	1 (1.2%)	1 (2.2%)	0	0

Source: NKF Spring Clinical Meeting

Exhibit 4
Patent Expiry Dates of Select Biologics in U.S.

Biologic	Type	U.S Expiry Date
Avastin	Humanized Antibodies	July 2019
Herceptin		June 2019
Humira		December 2016
Synagis		October 2015
Erbitux	Non-Humanized Antibodies	February 2016
Remicade		September 2018
Rituxan		September 2016
Aranesp	Not Antibodies	May 2024
Avonex		2015
Enbrel		November 2028
Epogen		August 2013
Neulasta		October 2015
Neupogen		December 2013
Lantus		2014
Lovenox		Expired

Source: Hospira reports NKF Spring 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 + extension	Establish an extended dose	80%, 90%, and 94% 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

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DOW JONES: 17,712.66
S&P 500: 2,061.02
NASDAQ: 4,891.22

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Market Perform (Hold)	32	Market Perform (Hold)	2
Underperform (Sell)	2	Underperform (Sell)	0

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