William Blair

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ZS Pharma, Inc.

NEJM Letters to the Editor Reinforces ZS-9's Onset-of-Action Differentiation

- After the markets closed Wednesday, April 15, *The New England Journal of Medicine* published new online material that included several letters to the editor and subsequent correspondence about previous publications in the journal on both Relypsa's (RLYP $36.79) patiromer and ZS Pharma's ZS-9 products for hyperkalemia entitled "New Agents for Hyperkalemia." Overall, we view these concerns raised by medical professionals to be a significant positive for ZS-9, where the majority of issues raised for patiromer questioned the trial study design and population enrollment whereas questions related to ZS-9 were mainly focused on active comparators (which were also a question with patiromer). In addition, ZS-9's publication on the fast onset-of-action in severe hyperkalemia patients continues to be a distinct differentiator that strengthens our belief that it is a best-in-class therapy.

- In the first note, Dr. Robet Phillips, Dr. Lawrence Appel, and Dr. Joy Weinberg stated that the low baseline rate of use of loop diuretics (32% of patients) in the patiromer study published by Weir et al. in the January 15 issue of *New England Journal of Medicine* was "noteworthy and might limit the clinical applicability of their finding that patiromer was effective in reducing hyperkalemia in patients with chronic kidney disease receiving RAAS inhibitors." The authors cited the African American Study of Kidney Disease and Hypertension that enrolled 1,094 black patients and showed that 75% of patients were receiving a concomitant loop diuretic and such diuretic use was associated with a decrease of 59% in the risk of hyperkalemia (during 3.0 to 6.4 years of follow-up, only 80 hyperkalemic events in 51 patients or less than 5% were identified). The authors suggested that a subgroup analysis stratified by loop-diuretic use in the patiromer studies would be informative. The authors of the study (Dr. Matthew Weir, Dr. George Bakris, and Dr. Bertram Pitt) responded by suggesting that loop diuretics can introduce volume depletion and increase the risk of gout and are not ideal when the primary purpose is to lower serum potassium levels. The authors further stated that 54% of patients were receiving diuretics and 9% were receiving mineralocorticoid antagonists and pointed to other adverse effects in the AASK study. We also note that the initial letter referenced a study involving African Americans, a population not included in the patiromer clinical trials, which enrolled primarily Caucasian subjects.

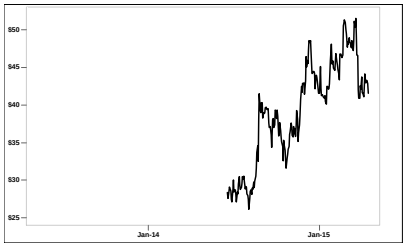
Stock Rating:	**Outperform**
Company Profile:	**Aggressive Growth**
Price Target:	$75.00
Symbol:	ZSPH (NASDAQ)
Price:	$42.00 (52-Wk.: $26-$53)
Market Value (mil.):	$1,068
Fiscal Year End:	December
Long-Term EPS Growth Rate:	
Dividend/Yield:	None

	2014A	2015E	2016E
Estimates			
EPS Q1	$0.02	$-0.93	NA
Q2	$-4.72	$-0.95	NA
Q3	$-0.81	$-1.00	NA
Q4	$-0.98	$-1.02	NA
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.)	24
Average Daily Volume	265,481

Financial Data (FactSet)	
Long-Term Debt/Total Capital (MRQ)	0.0
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 the second note, Dr. Thomas Finucane asked how physicians felt justified in sending patients home with potassium levels as high as 6.4 mmol per liter without a specific established treatment. In response to this letter, the authors cited their Special Protocol Agreement with the FDA and that mean serum potassium levels were less than 5.5 mmol per liter two days after the start of treatment and that significant early decreases were reported at seven hours in patients with moderate-to-severe hyperkalemia. We continue to believe that onset-of-action is a clear differentiator between ZS-9 (K lowering within hours) and patiromer (beyond 48 hours). In another letter to the editor published Wednesday entitled "Sodium Zirconium Cyclosilicate for Urgent Therapy of Severe Hyperkalemia," ZS-9 trial study authors Dr. Mikhail Kosiborod, Dr. W. Frank Peacock, and Dr. David Packham examined a subset of 45 patients with baseline serum in the range of 6.1 to 7.2 mmol per liter receiving a 10g dose of ZS-9. The mean serum at baseline of 6.3 mmol per liter declined by 0.4 mmol per liter at 1 hour, 0.6 mmol per liter at 2 hours and 0.7 mmol per liter at 4 hours ($p<0.001$ for the comparison of each time point with baseline) after a single 10 g dose of ZS-9. The median time to serum potassium less than 6.0 mmol per liter was 1.07 hours and the median time to a level below 5.5 mmol per liter or less was 4.00 hours. In addition, by 4 hours, 80% of patients had a serum potassium level that was less than 6.0 mmol per liter and 52% had a level that was 5.5 mmol per liter or less. There were no serious adverse events nor were there any cases of hypokalemia (less than 3.5 mmol per liter). In our view, these two letters highlight the need for a rapid onset of action and an awareness of this in the community, two trends which should aid reception of ZS-9 and likely be a liability to patiromer in the marketplace.

- In the third letter to the editor, Dr. Arkady Synhavsky commented on the omission of fludrocortisone as a cheap and long-term therapy. We also note that this question came up at the recent National Kidney Foundation Spring Clinical Meetings. Both Dr. Weir et al. and Dr. Packham et al. responded to the comment by noting the sodium retention, association with several severe adverse events (renal insufficiency, heart failure, and hypertension) with fludrocortisone as well as the fact that it is not indicated for hyperkalemia, and that the aldosterone-like effects would defy the purpose of RAAS inhibition. The fourth letter from Dr. Christina Yuan, Dr. Dustin Little, and Dr. Robert Nee noted an incorrect citation of their studies in both Weir and Packham NEJM publications and suggested that sodium polystyrene sulfonate (SPS) be used as active comparator in future clinical trials with ZS-9 and patiromer. Dr. Weir et al. respond to the letter by saying that their study did not include SPS as a comparator due to warnings, precautions, and sodium load. Dr. Packham and colleagues responded by speaking to the association with colonic necrosis, and GI side effects. As we have noted in the past, SPS has not been approved under the modern FDA standards and likely would have been a liability in enrollment and patient retention if the product was used as a comparator. We believe SPS is primarily utilized due to the lack of effective, well-studied therapies, such as the current agents under development.

- Following the publication of these physician letters, we continue to believe that ZS-9 holds a best-in-class profile for the treatment of hyperkalemia and continue to rate ZS Pharma as Outperform with a price target of $75. *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, which we believe may occur in the near term. We continue to view ZS Pharma as a top idea in 2015.*

Valuation

We rate ZS Pharma as 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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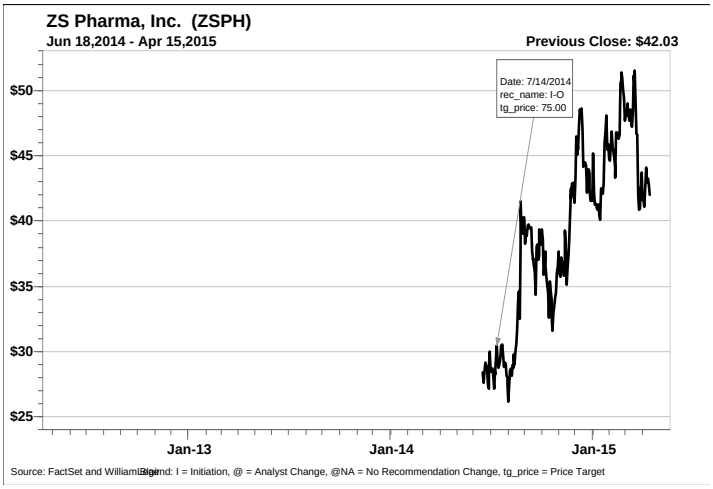
DOW JONES: 18,036.70
S&P 500: 2,095.84
NASDAQ: 4,977.29



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Coverage Universe	Percent	Inv. Banking Relationships*	Percent
Outperform (Buy)	65	Outperform (Buy)	16
Market Perform (Hold)	33	Market Perform (Hold)	3
Underperform (Sell)	2	Underperform (Sell)	0

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