William Blair

ZS Pharma, Inc.

February 19, 2015

Ahead of Long-Term Safety Data from ZS-9, We View Patiromer Safety Profile as Low Hurdle; Remain Outperform

- As we approach the filing of the ZS-9 NDA for the treatment of hyperkalemia (HK) and maintenance of normokalemic levels, we are revisiting the product profiles of ZS-9 and the competitive potassium binder patiromer by Relypsa (RLYP $36.05). Ahead of ZS Pharma's filing of its NDA, which is expected during the first half of 2015, we continue to expect the company to announce results from its long-term efficacy and safety studies, ZS004E (N=258) and ZS005 (N=500) near the middle of the year. As we believe hyperkalemia competitor Relypsa has become more prominent in its positioning against ZS-9, we would like to revisit the profiles of both products. While patiromer holds some benefits over ZS-9, namely being two quarters ahead of ZS-9 to market and being a nonmetal-based binder (which we believe is more of a Street issue versus an eventual marketing issue), patiromer also holds an improved rate of edema, which Relypsa often notes in press releases; however, we believe other issues with the patiromer dataset look more concerning than an edema rate in a dose (15g) which may be used by, at most, 10% of patients. Overall, we believe the benefits held by patiromer are outweighed by concerns coming out of the patiromer long-term data and the product profile of the compound which we describe in the following.

- **Death Rate in Patiromer Long-Term Safety Data Likely Higher Than ZS-9.** The patiromer long-term safety data included a relatively high death rate of 15 patients (4.9%) in a relatively small clinical trial (N= 304). Given the size of the ZS Pharma long-term studies (N=258 for ZS004E and N=500 for ZS005), a total of 37 deaths would have to occur over both studies to approach the rate observed with patiromer, a number we believe is highly unlikely, as management has recently made public commentary of no deaths in either study. With only a few months of treatment left prior to the company filing with the FDA, we believe there is a high likelihood ZS-9 should hold a reduced death rate versus patiromer in its long-term safety data. Although cross-trial comparison is normally difficult, especially given the different patient populations (79% of enrollment from Eastern Europe in Relypsa's OPAL-HK study versus the U.S.-based HARMONIZE and ZS003 studies), we continue to believe ZS-9 holds an attractive comparative profile. Given the number of deaths due to cardiovascular issues in the patiromer long-term safety dataset, we believe it is worth revisiting hypomagnesemia rates and the amount of calcium being dosed with patiromer, as both may influence long-term cardiac safety.

Stock Rating:	**Outperform**
Company Profile:	**Aggressive Growth**
Price Target:	$75.00
Symbol:	ZSPH (NASDAQ)
Price:	$46.62 (52-Wk.: $26-$50)
Market Value (mil.):	$964
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.)	21
Float (mil.)	10
Average Daily Volume	193,297

Financial Data (FactSet)	
Long-Term Debt/Total Capital (MRQ)	0.0
Book Value Per Share (MRQ)	5.5
Return on Equity (TTM)	-235.2

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.

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- **While an independent SRB reviewed all deaths and noted that none were related to the study drug, it is difficult to ignore the adverse cardiovascular effects, given patiromer's effects on calcium and magnesium.** In our original initiation report, we noted the higher affinity for patiromer to bind magnesium versus potassium and the relatively high rate of hypomagnesemia in the company's PEARL-HF study (24%). It is also interesting to note the lower rates observed in OPAL-HK (3%-4%) versus PEARL-HF. A deeper look into the data suggests that a change in the definition of hypomagnesemia from the PEARL-HF study to the OPAL-HK study likely aided this decreased rate of hypomagnesemia. As shown in exhibit 1, in the PEARL-HF study, patients were considered to have reduced serum Mg2+ concentrations at values less than 1.8 mg/dL. This yielded 24% of patients treated with patiromer in the study with hypomagnesemia, compared with 2.1% in placebo, a statistically significant difference. In the OPAL-HK study, hypomagnesemia was defined as serum Mg2+ of less than 1.4 mg/dL, and the resulting hypomagnesemia level dropped to only 3% of patiromer-treated patients, according to the more strict definition. In addition, 4% of patients in the patiromer group received magnesium-replacement therapy during the initial treatment phase. Our review of the literature on hypomagnesemia suggests this 1.4 mg/dL rate is a relatively low threshold which was not utilized in any of the publications we reviewed. We note that a publication titled "Hypomagnesemia and the Risk of Death and GFR Decline in Chronic Kidney Disease" by Van Laecke S, published in September 2013, uses a 1.8 mg/dL threshold, while high serum magnesium was defined as 2.2 mg/dL. We note the difference in this publication between hypomagnesemia and high magnesium blood serum levels (0.4 mg/dL) was the same difference between the definitions of hypomagnesemia between OPAL-HK and PEARL-HF.

- **A comparison with Renagel/Fosrenol, in our opinion, is inaccurate.** We have often heard comparisons between the patiromer and ZS-9 to the phosphate-binder market. During the marketing of Genzyme's Renagel (sevelamer hydrochloride), the life cycle of that franchise faced competition from Shire (SHPG $237.64; Outperform) and its rare earth-metal-based phosphate binder, Fosrenol (lanthanum carbonate). A metal-based marketing message was effective during the Shire and Genzyme competition for share of the phosphate-binder market with Fosrenol sales in 2013 roughly $183 million and sales of Renvela/Renagel in 2013 roughly $777 million. However, we see some key differences between the Renagel and Fosrenol marketing battles, namely the best-in-class safety and efficacy profile of ZS-9 in the short term and long term. In addition, Genzyme with Renagel had entered the market with a six-year lead time versus Shire's Fosrenol (Renagel was first approved in 1998, while Fosrenol entered the market six years later, following an approval in October of 2004). Given our view that ZS Pharma should potentially be able to point to a lower death rate in its long-term safety study, less exposure to calcium, and reduced risk of hypomagnesemia, we believe the Renagel/Fosrenol comparison is not relevant to the hyperkalemia market.

- **Potential vascular calcification by patiromer should raise concerns in market.** We also note the relatively high load of calcium which comes with patiromer dosing. At an average dose of 12.8g for mild HK patients (<5.5) and 21.4g for patients in the high HK group (>5.5), total daily dose of total drug product for those dose groups is 3 sachets or 21 grams for mild HK patients and 5 sachets or 35 grams for high HK patients. This would correlate to 2.4g calcium and 6g sorbitol in the mild HK patients or 4g calcium and 10g sorbitol for the high HK patients, given the patiromer formulation. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines state that total elemental calcium intake should not exceed 2 g/day to prevent vascular calcification, and a more reasonable recommendation may be a calcium intake of less than 1.4 g/day, with further restriction in diabetes due to a higher burden of calcification (Patel and Singh, *Semin Nephrol* 2009; Mehrotra R et al. *Kidney Int* 2005). Given the significant amount of calcium in patiromer, we believe vascular calcification fears could raise flags during the regulatory review and/or marketing of patiromer, and the K/DOQI recommendations could give the yield the entire diabetes hyperkalemia market to ZS-9. While Relypsa management will likely point to its belief that free calcium is not available until the colon and is not absorbed systemically, we do not believe this fully describes how binders normally travel through the GI tract, and publications by Relypsa in the past have noted, "As RLY5016 traverses the gut it exchanges monovalent (Na) and divalent cations (Ca, Mg) and then preferentially binds K+ in the colon where the concentration of this cation is substantially higher than that of Na+, Ca2+ or Mg2," suggesting free calcium in the GI tract prior to the colon. (Buysse, JM; *Future Cardiology* 2013).

- **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, which we believe may occur in the near term. We continue to view ZS Pharma as a best pick in 2015.

Exhibit 1
Definition of Hypomagnesemia in PEARL-HF and OPAL-HK (Replysa Clinical Trials) and Reported Events

	PEARL-HF	OPAL-HK
Hypomagnesemia Definition	serum Mg2+ <1.8 mg/dL	serum Mg2+ <1.4 mg/dL
Rate of Hypomagnesemia reported	24% of patients treated with patiromer vs. 2.1% in placebo, statistically significant decrease from baseline was observed (-0.22 vs. 0.01 mg/dL for the patiromer and placebo groups respectively, P<0.001)	A serum magnesium level of less than 1.4 mg per deciliter (0.58 mmol per liter) occurred in eight patients (3%) during the initial treatment phase and through its follow-up period. Magnesium-replacement therapy was initiated in nine patients (4%) in the patiromer group during the initial treatment phase.

Sources: Pitt et al. Eur Heart J 2011, Weir et al. NEJM 2014

Additional Details:

Our View on the Upcoming K+ Wars

With Relypsa's patiromer NDA being filed, accepted by the FDA, and granted a PDUFA date of October 21, we are revisiting our belief that ZS-9 represents, although potentially not the first to market, a best-in-class product for the treatment of hyperkalemia and maintenance of normokalemic levels. While Relypsa management has publically guided that it does not expect an advisory committee ahead of its PDUFA date, we believe this is likely aggressive guidance, given the new class of therapies, new mechanism of action, chronically ill patient population, and what we believe is a long term safety dataset with a relatively high death rate.

We continue to view ZS Pharma's ZS-9 as a best-in-class product ahead of the filing of its NDA, which is expected during the first half of 2015. After the filing, management should be in a position to announce results from their long-term efficacy and safety studies, ZS004E (N=258) and ZS005 (N=500), near the middle of the year, suggesting a PDUFA date in mid-2016. While patiromer does indeed hold some benefits over ZS-9, namely the focus of Relypsa management on not being a metal-based binder, we view this issue as more of a Street issue versus an eventual marketing liability. ZS-9 is based on a proprietary matrix of zirconium silicate, and we acknowledge that if both ZS-9 and patiromer are approved during the 2015-2016 timeframe, Relypsa will likely seek to differentiate patiromer from ZS-9 by focusing on the metal basis of the therapy.

We Believe an Advisory Committee for the Class of Hyperkalemia Drugs Is Still Very Possible

As management from Relypsa continues to cite the fact that the FDA has not scheduled an advisory committee for patiromer, we do note that advisory committees have been called relatively late in product review process in the past, especially with the Cardiovascular and Renal Drugs Advisory Committee. In addition, we believe the FDA may be incentivized to call for an advisory committee after officially receiving ZS-9's NDA filing, which we expect to occur in the March-April timeframe. Given the death rate observed in AMETHYST-DM, we believe the company may still be notified of an advisory committee roughly four months ahead of the company's PDUFA date, which suggests an advisory committee may still be announced until June 15, ahead of the company's October 15 PDUFA date.

Long-Term Patiromer Data Provides a Relatively Achievable Bar for ZS-9 Long-Term Safety Due to Increased Death Rates

At a late December conference, the Cardiovascular Clinical Trialists Forum (CVCT), Relypsa presented long-term safety data from patiromer which we believe provides a relatively achievable bar for the safety profile of ZS-9 ahead of results from the ZS004E and ZS005, which may be available to the Street by midyear. As we believe ZS Pharma's competitor continues to point towards the edema rate for ZS-9, we believe a close look at the patiromer long-term safety data suggests several discrepancies which may be more concerning than the edema rates in HARMONIZE. In HARMONIZE, edema was observed in the ZS-9 10-gram arm (N=3, 6%), ZS-9 15-gram dosage arm (N=8, 14%) with reported edema versus the placebo arm (N=2, 2%) and the 2-gram arm (N=2, 2%).

In the patiromer one year safety study, AMETHYST-DN, a relatively high death rate occurred, with 15 deaths out of 304 patients (4.9%), 11 due to cardiovascular causes. While none were considered related to the study drug by the company's independent SRB, we continue to believe this event rate may be a risk during the company's regulatory review. We have included safety results from AMETHYST-DM in exhibit 2. While ZS004E and ZS005 are still blinded, management has publically stated that no deaths have been reported to date in the long-term safety portion of its 758 patients across both studies.

Exhibit 2
AMETHYST-DN Safety Study Results

Category	mild HK (N=220)	moderate HK (N=84)	Comments
Serious AEs	29 (13%)	15 (18%)	None were attributed to patiromer by PI
Deaths	N=15		11 out of 15 due related to CV causes Sudden cardiac death, N=7 Acute MI, N=4
Hypomagnesemia	26 (9%) 13 (4%) of patients had serum Mg2+ <1.2 mg/dL		Reported based on PI assessment; may not have correlated with lab values
	15 (7%)	11 (13%)	
Worsening of HTN	14 (6%)	11 (13%)	
Worsening of CKD	14 (6%)	10 (12%)	
Diarrhea	12 (6%)	14 (17%)	
Constipation	11 (5%)	5 (6%)	
Hypoglycemia	4 (2%)	8 (10%)	Based on PI assessment; may not have correlated with lab values

Source: Cardiovascular Clinical Trialists Forum 2014 Poster

We Believe That Differences in Hypomagnesemia Rates in Patiromer Clinical Trials May Be Due to a Change in Definition.

Decreasing rates of hypomagnesemia observed with patiromer between the PEARL-HF and OPAL-HK studies look to be aided by changes in definitions. When examining the publication for patiromer, there was a change in the definition of hypomagnesemia from the PEARL-HF study to the OPAL-HK study. As shown in exhibit 1, in the PEARL-HF study, patients were considered to have reduced serum Mg2+ concentrations at values less than 1.8 mg/dL. This yielded 24% of patients treated with patiromer in the study with hypomagnesemia, compared with 2.1% in placebo, a statistically significant difference. However, in the OPAL-HK study, hypomagnesemia is defined as serum Mg2+ of less than 1.4 mg/dL, where only 3% of patiromer-treated patients were included in this definition. In addition, 4% of patients in the patiromer group received magnesium-replacement therapy during the initial treatment phase. We believe that the change in definition from study-to-study, as well as the replacement therapy introduced in the initial treatment phase, may have also contributed to the reported decreases in hypomagnesemia rates. A paper examining nine studies on hypomagnesemia showed that most of the studies defined hypomagnesemia as ≤ 1.7 mg/dL or <1.7 mg/dL, with one study defining it slightly higher (<1.8 mg/dL) and one study defining it slightly lower (<1.6 mg/dL) (Park et al. *PLoS One* 2014).

We continue to view ZS-9 as holding an improved product profile over patiromer based on what we view as a higher-quality clinical program. However, we note that both products seem effective, and we view the hyperkalemia market as large enough to support two successful products, if both are approved.

The ZS-9/Patiromer Debate Is Very Different from Renagel/Fosrenol

A similar strategy was used by Genzyme, now part of Sanofi, during the marketing of Renagel (sevelamer hydrochloride); the life cycle of that franchise faced competition from Shire and its rare earth-metal-based phosphate binder, Fosrenol (lanthanum carbonate). The marketing message was effective during the Shire and Genzyme competition for share of the phosphate-binder market. Fosrenol sales in 2014 were about $183 million, while sales of Renvela/Renagel were about $777 million in sales. However, we see some key differences between the Renagel and Fosrenol marketing battles. Namely, we believe ZS-9 will have best-in-class short-term and long-term data (which we detail later). We see the datasets of ZS-9 versus Patiromer more different than the Renagel/Fosrenol market dynamics. Genzyme with Renagel had entered the market with a six-year lead time versus Shire's Fosrenol (Renagel was first approved in 1998, while Fosrenol entered the market six years later following an approval in October of 2004). The chewable Fosrenol also was likely an unpleasant formulation for ingestion in doses up to 1.5 grams to 3 grams with every meal, while the two to four 400mg or 800mg tablets of Renagel, while not pleasant either, were often mentioned by physicians as having a taste preference over the metal-based Fosrenol.

Zirconium Has a Long History of Use in Biomedical Applications and Consumer Products

The daily zirconium intake of a normal U.S. citizen is likely to be about 1 milligram to 9 milligrams. Experimental toxicity studies of zirconium demonstrate that the metal is inert and has low toxicity. We have listed some common products with zirconium and a history of safe usage in humans in exhibits 2 and 3. However, the most applicable use for zirconium, considering the hyperkalemia patient population, is the use of the metal in millions of hemodialysis columns since the 1970s and as knee and hip replacements.

Exhibit 3
ZS Pharma, Inc.
Zirconium-Containing Products

Product	Amount	Relative to ZS-9
85g Antiperspirant Stick	2295 mg	8,196,429x
Soil	300 mg/L	1,071,429x
Human Body Content	300 mg	1,071,429x
Daily Food Content	3.65 mg	13,036x
Zr From Four-Hour Sorbent Hemodialysis	0.758 mg	2,707x
Daily Drinking Water Content	0.65 mg	2,321x
Sea Water	0.004 mg/L	14x
Soluble From 10 g ZS-9	0.00028 mg	1x

Source: Company reports

Exhibit 4
ZS Pharma, Inc.
History of Safe Zirconium Uses in Humans

Most comprehensive study of Zr was conducted by Schroeder and Balassa, Lee recently reviewed current biomedical uses
Daily Zr intake is estimated to be 1-9 mg per day
Experimental toxicity studies demonstrate that Zr is inert and has low toxicity, making it well suited for biomedical applications
Zirconium-containing compounds safely used in many biomedical applications
Nephrology (hemodialysis, peritoneal dialysis, hemofiltration)
Dental implants and other restorative practices
Middle ear ossicular chain reconstruction
Safely used in Patients with CKD
Millions of dialysis treatments with REDY and SORB columns since 1970s
Fresenius developing new Zr based DIALISORB column
Fresenius developing Zr based wearable artificial kidney

Sources: Company reports, Schroeder *J. Chron. Dis.* 1966, Lee *ASAIO Journal* 2010 Ash *Seminars in Dialysis* 2009.

For ZS-9, we believe the satchel of drug which may be stirred into a glass of water with no taste is an improved formulation over the original phosphate-binder formulation. Patiromer is also a dry odorless powder that is dosed with calcium, which could have an effect on the binding of potassium. Calcium-based binders are also used as a relatively cheap alternative to Renagel and Fosrenol; however, both Genzyme and Shire have incorporated in their marketing message the potential negative cardiovascular outcomes of calcium-based products being used in patients with poor cardiovascular health. This message may still linger in the chronic kidney disease markets and could be a liability for patiromer. *Overall, we believe the benefits held by patiromer are outweighed by concerns coming out of the patiromer long-term data and the product profile of the compound, which we describe in the following.*

Calcium in Patiromer Above Recommended K/DOQI Guidelines

Following what we believe are unresolved issues with the rate of hypomagnesemia in the use of patiromer, we also note the high rates of calcium being used in patiromer patients. At an average dose of 12.8g for mild HK patients (<5.5) and 21.4g for patients in the high HK group (>5.5), total daily dose is 3 sachets and 5 sachets, respectively or 21 grams and 35 grams of total drug product for those dose groups. This would correlate to 2.4g calcium and 6g sorbitol in the mild HK patients or 4g calcium and 10g sorbitol for the high HK patients, given the patiromer formulation.

K/DOQI guidelines state that total elemental calcium intake should not exceed 2 g/day to prevent vascular calcification, and a more reasonable recommendation of calcium intake should be less than 1.4 g/day, with further restriction in diabetes due to a higher burden of calcification (Patel and Singh, *Semin Nephrol* 2009; Mehrotra R et al. *Kidney Int* 2005). Given the significant amount of calcium in patiromer, we believe vascular calcification fears could be a very effective marketing message for ZS-9 and may potentially raise flags during the regulatory review of patiromer. While we believe Relypsa management points toward the cation exchange for calcium and potassium likely occurring in the colon, we believe that free calcium is likely available for absorption prior to the colon. Specifically, publications by Relypsa in the past have noted that patiromer will "ionize under pH conditions present along the extent of the GI tract, particularly in the colon" and "as RLY5016 traverses the gut it exchanges monovalent (Na) and divalent cations (Ca, Mg) and then preferentially binds K+ in the colon where the concentration of this cation is substantially higher than that of Na+, Ca2+ or Mg2," suggesting free calcium in the GI tract prior to the colon (Buysse, JM; *Future Cardiology* 2013). We believe that language suggests that while a majority of binding occurs in the colon, there is likely free cation available throughout the GI tract.

Bardoxolone Methyl Phase III Study Termination in More Progressed Chronic Kidney Disease (CKD) Patients Due to Death Rates That Were Lower Than AMETHYST-DN

While it is difficult to find comparable studies to judge the patiromer 4.9% death rate observed in its long-term safety study, we note the results of the well-publicized phase III clinical trial termination in patients with end stage renal disease (ESRD) and Type 2 diabetes treated with bardoxolone methyl showed a much lower rate of death from cardiovascular causes—2.5% in active versus 1.7% in placebo. When comparing these results with AMETHYST-DN at a high level, while it is always difficult to compare different clinical trials, we see a higher death rate with patiromer's long-term safety data (4.9%) in less-progressed CKD patients (GFR in AMETHYST-DN: Mild HK = 42 ml/min/1.73m^2 and Moderate HK = 36 ml/min/1.73m^2 versus Bardoxolone methyl GFR = 22.5 ml/min/1.73m^2).

Conclusion
We believe that the last several events (CVCT poster, the presentation of HARMONIZE at AHA, JAMA/NEJM publications, and ZS Pharma's 2014 analyst event) have further solidified our view that ZS-9 represents a best-in-class therapy of the treatment of hyperkalemia. We believe that the ZS Pharma's robust dataset at the time of its potential NDA submission in the first half of 2015 (with about 1500 tested patients expected, with patients results out to one year) may be a differentiating factor in a potential advisory committee meeting with the FDA.

In Appendix 1, we provide a summary of the clinical trials published to date for ZS-9 and patiromer. We believe the NEJM publications continue to show a significantly differentiated onset-of-action profile for ZS-9 with a median time-to-normalization reported by the company at 2.2 hours. Although questions on longer-term efficacy and safety remain (over four weeks), we believe the company is adequately addressing the issue with its open-label extension study (ZS004E) and one year safety study (ZS005) set to read out in 2015.

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 in select markets.

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

Our models are included on the following pages.

Appendix I
ZS-9 and Patiromer FOS Clinical Trial Publication Summary

	ZS-9		Patiromer FOS	
	ZS003	HARMONIZE	PEARL-HF	OPAL-HK
Citation	Packham et al. *NEJM* 2014	Kosiborod et al. *JAMA* 2014	Pitt et al. *Eur Heart J* 2011	Weir et al. *NEJM* 2014
Number of Patients Enrolled	Initiation phase: 753 patients (158 placebo, 154 1.25g, 141 2.5g, 158 5g, 143 10g), Maintenance Phase: 543 patients (216 placebo, 94 1.25g, 104 2.5g, 65 5g, 63 10g)	Initiation phase: 258, Randomized Phase: 237 (45 - 5g, 51 - 10g, 56 - 15g, 85 - placebo)	105 (56 patiromer, 49 placebo)	243 patients: single-arm initiation (92 with mild hyperkalemia, 151 with moderate/severe); 107 patients: randomized withdrawal phase, 55 patiromer, 52 placebo
Underlying Etiologies	Hyperkalemia, regardless of underlying etiology	Hyperkalemia, regardless of underlying etiology	CHF, CKD, RAASi	CKD, RAASi, Diabetes, CHF (no Class IV)
Baseline Mean Serum K+	Initation Phase: 5.3 mEq/L, Maintenance Phase: 4.7 mEq/L (placebo/5g), 4.45 mEq/L (placebo/10g)	Initiation phase: 5.6 mEq/L, Maintenance phase: 5.55 mEq/L (placebo), 5.53 mEq/L (5g), 5.58 mEq/L (10g), 5.55 mEq/L (15g)	4.69 mEq/L for patiromer group, 4.65 mEq/L in placebo	Initiation phase: Mild Hyperkalemia: 5.3 mEq/L, Moderate-to-Severe Hyperkalemia: 5.7 mEq/L; Withdrawal phase: 4.45 mmol/L in placebo, 4.49 mmol/L in patiromer
Treatment Duration	48 h initiation phase, 12 day maintenance phase (2 weeks total)	48 h initiation phase, 26 day maintenance phase (4 weeks total)	28 days (4 weeks)	4 week single-group, single-blind initial treatment phase and 8 week placebo-controlled, single-blind, randomized withdrawal phase (12 weeks total)
Dosing Regimen	Initiation phase: 10g t.i.d. for 48 hr, Maintenance Phase: placebo, 1.25g, 2.5g, 5g, 10g, q.d for days 3-15	Initiation Phase: 10g t.i.d. for 48 hr, Withdrawal Phase: 5g, 10g, 15g, or placebo q.d. for days 8-29	15g in AM and PM (b.i.d.), 30g total	Initation phase: mean daily dose of 12.8g in mild HK, 21.4g in mod-to-sev HK
Primary Endpoint	Initiation Phase: mean serum potassium, Maintenance Phase: mean serum potassium	Initiation phase: mean serum potassium, Maintenance Phase: Percent of normokalemic patients	Mean change of serum K+ from baseline to day 28	Mean change of serum K+ from baseline to day 28, Mean change in serum K+ in withdrawal phase (week 8)
Mean Serum K+ at Primary Endpoint	Initiation Phase: 5.05 mEq/L (placebo), 4.84 mEq/L (2.5g), 4.76 mEq/L (5g), 4.57 mEq/L (10g), Maintenance Phase: 4.78 mEq/L (5g) vs. 4.95 mEq/L (placebo); 4.59 mEq/L (10g) vs. 5.01 mEq/L (placebo)	Initation phase: 4.5 mEq/L, Withdrawal Phase: 5.1 mEq/l in placebo, 4.8 mEq/L in 5g, 4.5 mEq/L in 10g, 4.4 mEq/L in 15g	4.47 mEq/L for patiromer, 4.88 mEq/L in placebo	Initiation phase: Mild Hyperkalemia: 4.65 mEq/L, Moderate-to-Severe Hyperkalemia: 4.47 mEq/L; Withdrawal phase: 4.49 mEq/L in patiromer group, 5.17 mEq/L in placebo
% of Normokalemic Patients	Initiation Phase: 75% 2.5g, 90% 5g, 99% 10g	Initiation phase 98% at 48 h, Withdrawal phase: 80% 5g dose, 90% 10g dose, 94% 15g dose, 46% placebo	93% (patiromer) vs 75% (placebo)	Initiation Phase: 74% (mild HK) and 77% (mod-to-sev HK); Withdrawal Phase: 85% (patiromer) vs. 40% (placebo)

Sources: Packham et al. NEJM 2014, Kosiborod et al. JAMA 2014, Pitt et al. Eur Heart J 2011, Weir et al. NEJM 2014, William Blair & Company, L.L.C.

William Blair

ZS Pharma
Earnings Model
2/19/15
($ in millions except EPS data)

Rating: Outperform
Company Profile: Aggressive Growth
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	2012(A)	2013(A)	Q1(A)	Q2(A)	Q3(A)	Q4(E)	2014(E)	2015(E)	2016(E)	2017(E)	2018(E)	2019(E)
ZS-9	-	-	-	-	-	-	-	-	36,767	218,357	445,814	740,445
Royalty/Milestone Revenue	-	-	-	-	-	-	-	-	-	-	-	-
Total Revenue	-	-	-	-	-	-	-	-	36,767	218,357	445,814	740,445
yr/yr growth	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	104.2%	66.1%
q/q growth			NA	NA	NA	NA						
incremental rev q/q												
Cost of Goods Sold	-	-	-	-	-	-	-	-	3,677	21,836	44,581	74,044
Gross Profit	-	-	-	-	-	-	-	-	33,090	196,521	401,233	666,400
SG&A	1,148	7,686	1,053	4,554	5,699	5,500	16,806	22,000	44,000	88,000	102,537	148,089
Growth							30%	20%	100%	100%	76%	15%
R&D	6,989	24,508	1,394	9,976	10,923	11,000	33,293	45,000	54,000	62,100	68,310	71,726
Growth		251%	-	-	-	-	36%	20%	20%	15%	10%	5%
Total Operating Expenses	8,137	32,194	2,447	14,530	16,622	16,500	50,099	67,000	98,000	150,100	170,847	219,814
growth			NA	NA	NA	NA	56%	34%	46%	53%	14%	29%
Operating Income	(8,137)	(32,194)	(2,447)	(14,530)	(16,622)	(16,500)	(50,099)	(67,000)	(64,910)	46,421	230,385	446,586
EBIT Margin							NM	NM	NM	NM	52%	60%
growth y/y (%)			NA	NA	NA	NA	NM	NM	NM	NM	NM	NM
Depreciation and Amortization	-		250	250	250	250	1,000	1,000	1,000	1,000	1,000	1,000
EBITDA	(8,137)	(32,194)	(2,197)	(14,280)	(16,372)	(16,250)	(49,099.0)	(66,000.0)	(63,909.7)	47,421	231,385	447,586
							NM	NM	NM	NM	52%	60%
Interest income	(17)	(31)		5	-31	225	199	750	600	800	1,200	1,400
Interest expense	2,099	9	(366)	(1,774)	272	750	3,000	2,000	1,500	1,500	1,000	1,000
Change in fair value of warrants	62	1,424										
Other	-	1										
Income Before Taxes	(10,281)	(33,597)	(2,813)	(16,299)	(16,863)	(17,025)	(53,000)	(68,250)	(65,810)	45,721	230,585	446,986
Income Tax Provision	-	-	(3,652)	-			(3,652)	1,000	1,000	16,460	78,399	151,975
Effective Tax Rate	0.0%	0.0%	NA	0.0%	NA	NA	NM	NA	NA	34%	34%	34%
Preferred stock accretion	(174)	(689)		(129)								
Net Income (loss) Attributable to Common	(10,455)	(34,286)	839	(16,428)	(16,863)	(17,025)	(49,348)	(69,250)	(66,810)	29,261	152,186	295,011
Net loss per share (diluted)	$ (2.63)	$ (8.52)	0.02	(4.72)	(0.81)	(0.81)	$ (3.28)	$ (2.96)	$ (2.72)	$ 1.17	$ 6.07	$ 11.52
Basic avg. number of shares used in computing net income	3,981	4,025	75,953	3,482	20,818	20,918	15,073	23,418	24,568	24,968	24,768	24,768
Diluted avg. number of shares used in computing net income	3,981	4,025	587,270	3,482	20,818	20,918	15,073	23,418	24,568	24,968	25,068	25,612
Key Ratios (GAAP unless noted)												
Gross Margin	NM	NM	NM	NM	NM	NM	NM	NM	NM	90.0%	90.0%	90.0%
R&D (% Total Rev.)	NM	NM	NM	NM	NM	NM	NM	NM	NM	28.4%	15.3%	9.7%
SG&A (% Total Rev.)	NM	NM	NM	NM	NM	NM	NM	NM	NM	40.3%	**23.0%**	**20.0%**
Operating Margin	NM	NM	NM	NM	NM	NM	NM	NM	NM	21.3%	51.7%	60.3%
Net Income Margin	NM	NM	NM	NM	NM	NM	NM	NM	NM	13.4%	34.1%	39.8%
Revenue Growth												
Growth Yr/Yr	NM	NM	NM	NM	NM	NM	NM	NM	NM	494%	104%	66%
Growth Q/Q	NM		NM	NM	NM	NM						
SG&A Growth												
Growth Yr/Yr	NM	570%	NM	NM	NM	NM	119%	31%	100%	100%	17%	44%
Growth Q/Q	NM		NM	NM	NM	NM						
R&D Growth												
Growth Yr/Yr	NM	251%	NM	NM	NM	NM	36%	35%	20%	15%	10%	5%
Growth Q/Q	NM		NM	NM	NM	NM						

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.

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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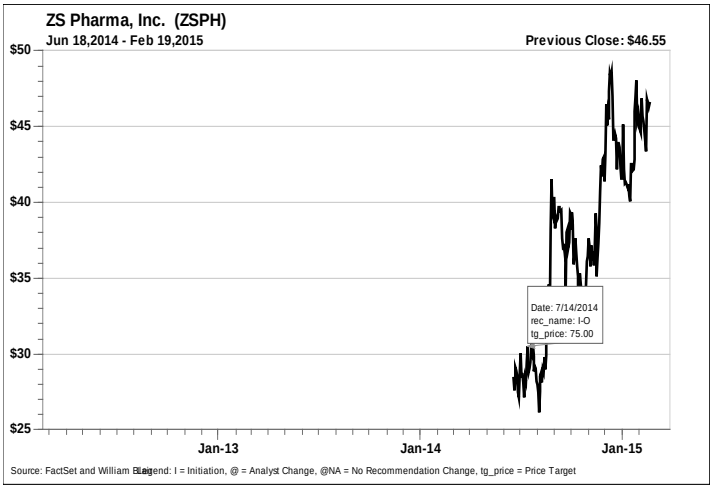
DOW JONES: 18,029.85
S&P 500: 2,099.68
NASDAQ: 4,906.36



Current Rating Distribution (as of 01/31/15)

Coverage Universe	Percent	Inv. Banking Relationships*	Percent
Outperform (Buy)	64	Outperform (Buy)	16
Market Perform (Hold)	32	Market Perform (Hold)	2
Underperform (Sell)	2	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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