William Blair

ZS Pharma, Inc.

September 23, 2014

Discussions With Hyperkalemia Key Opinion Leader Reinforce Views on Market Size and Need for New Treatments

We spoke with a key opinion leader (KOL) in the field of cardiology, Bertram Pitt, M.D., a physician from the University of Michigan Medical Center and scientific consultant for ZS Pharma competitor Relypsa (RLYP $21.50), regarding recent subgroup analysis data from ZS Pharma and Relypsa that was presented at the Heart Failure Society of America, the market potential of hyperkalemia, comparisons between the two therapies, and the upcoming Annual Meeting of the American Heart Association on November 15-19 in Chicago, where ZS Pharma will present its second Phase III trial (HARMONIZE) data.

Key Issues:

- **KOL views market as large enough for two players; both ZS Pharma and Relypsa represent a significant advancement from the current standard-of-care and open up chronic market.** While we have laid out our thesis that ZS-9 is in our view the best-in-class therapy for the treatment of hyperkalemia, our discussion with Dr. Pitt reinforces our belief that the treatment of hyperkalemia is a large market and suggests that both therapies in development, ZS-9 for ZS Pharma and patiromer for Relypsa, are a significant improvement over the current therapy available in the clinic, Kayexalate. This is primarily because of the multitude of adverse effects that have been shown to occur with Kayexalate, particularly in a sorbitol solution. As we also noted in our initiation report, in commentary published in the *Journal of the American Society of Nephrology* in 2012, Sterns et al. wrote that, "If Kayexalate or SPS in sorbitol were presented to the FDA as new drugs with data available today, it is doubtful that either would pass muster." Dr. Pitt noted potential use in chronic kidney disease patients, heart failure, and diabetes patients and stated that the market for hyperkalemia therapies is large in the chronic setting and two active marketers may find room for more than one successful therapy in the market.
- **The questions remaining for Relypsa concern the onset-of-action and for ZS Pharma revolve around long-term efficacy.** As ZS Pharma has presented data from the company's 753-patient Phase II/III study, ZS003, at multiple cardiovascular and diabetes medical meetings during 2014, Dr. Pitt is confident in the efficacy of ZS-9 over the time frame currently reported (14 days) and the side effect profile looks to be attractive, with a single-digit side effect profile to date. However, he is waiting for the company's 52-week data before speculating on the long-term safety and efficacy of the therapy. We believe data from the 52-week open label long-term study (ZS005) and the extension portion of ZS004 are highly anticipated, and should solidify the ability of ZS-9 use to maintain normokalemia in the long term. To date, the safety profile of ZS-9 has been shown to be a major clinically differentiating factor from patiromer and it remains to be shown if the profile continues in a long-term therapy setting. Dr. Pitt believes that due to the primary site of action between the two products, with patiromer active in the colon whereas ZS-9's site of binding is in the intestine, patiromer might not be the best product in the acute setting for rapid reduction of potassium levels. We believe this is a major differentiator; if ZS-9 were to show rapid lowering of potassium levels, it may prove the best therapy in the acute setting, and following long-term data, which should be available in 2015, the product may be ideal for rolling patients onto a maintenance therapy following an acute attack.

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

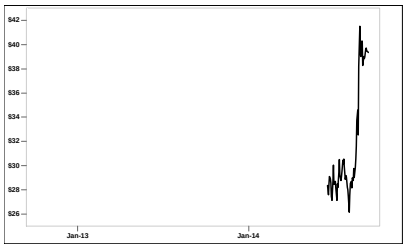
Stock Rating:	**Outperform**
Company Profile:	**Aggressive Growth**
Price Target:	$75.00
Symbol:	ZSPH (NASDAQ)
Price:	$34.36 (52-Wk.: $26-$43)
Market Value (mil.):	$715
Fiscal Year End:	December
Long-Term EPS Growth Rate:	
Dividend/Yield:	None

		2013A	2014E	2015E
Estimates				
EPS	Q1	NA	$0.02	NA
	Q2	NA	$-4.72	NA
	Q3	NA	$-0.74	NA
	Q4	NA	$-0.81	NA
	FY	$-8.52	$-3.18	$-2.94
	CY		$-3.18	$-2.94
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	167,970

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

- **Although not required by the FDA, the clinical community is very interested in the translational impact of both products' ability to reduce serum potassium on patient outcomes, which may be shown in post-marketing studies.** The majority of the patient populations who develop hyperkalemia have significant chronic diseases such as congestive heart failure (CHF), chronic kidney disease (CKD), and diabetes. As these patients are dosed with renin-angiotensin-aldosterone (RAAS) inhibitors, physicians may under-treat or even halt treatment altogether if serum potassium levels rise. For heart failure patients in particular, Dr. Pitt noted that cardiologists are very sensitive to potassium levels when prescribing therapy because of the known association between high serum potassium and acute cardiovascular events. Providing therapies to keep potassium levels in the normokalemic range should lead to improved clinical outcomes with aggressive RAAS inhibitor use in diabetics and mineralocorticoid receptor antagonists (MRA) use shown to lead to 22%-30% mortality benefits in heart failure patient populations. On our call, Dr. Pitt noted that a post-approval study could be conducted in high-risk patients (such as those with myocardial infarctions) that examined hospital readmissions or other clinical outcomes and could improve physician adoption of the class of drugs.

- **Regarding the upcoming American Society for Nephrology meeting, we will be looking for a continued drumbeat suggesting the importance of managing potassium levels, while HARMONIZE data will be the focus at the American Heart Association meeting in November.** In general, Dr. Pitt believes that nephrologists are less concerned with increased potassium levels until they reach 6.0 mEq/L, given the use of dialysis in the patient population, while cardiologists are more aware of the issues surrounding potassium levels over 5 mEq/L given the past clinical experience with MRAs. In general, he sees an increased awareness likely for targeting lower potassium agents, given the likely near-term availability of efficacious and safe agents (patiromer, ZS-9). Dr. Pitt will be the discussant for ZS Pharma's data from the HARMONIZE trial, which is set to be presented at the American Heart Association meeting in November, and we believe he will be looking for onset of action (if available) and safety from the data set. While he impressed by the tolerability of patiromer over 52 weeks, we will not have comparative long-term data from ZS-9 until mid-2015.

- While Dr. Pitt is very active in the development of ZS Pharma's main competitive compound, patiromer being developed by Relypsa, following our discussions with him we continue to view the market as large and underserved. We also continue to view ZS-9 as a best-in-class therapy. Given the well-documented prevalence and growing patient populations within CKD, CHF, diabetes, and individuals on RAAS inhibitors, we believe the potential market for ZS-9 is significant and while we view it as the best-in-class agent, considering the large market, several successful products may be able to be supported by the market. *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.*

Additional Information

ZS Pharma recently announced results of a subgroup analysis of heart failure patients from its previous Phase III clinical trial, ZS003. The data was presented as part of a late-breaking clinical trial oral session at the Heart Failure Society of America's Annual Meeting in Las Vegas. In the subgroup analysis, 147 normokalemic heart failure patients on RAAS (renin-angiotensin-aldosterone system) inhibitor therapy who received either 5 g or 10 g of ZS-9 once per day maintained serum potassium levels in the normokalemic range (between 3.5 mEq/L and 5 mEq/L) throughout the 12-day maintenance period with mean serum potassium of 4.7 and 4.5 mEq/L, respectively (exhibit 1, page 3). These levels were significantly lower than the placebo group for both the 5 g dose ($p<0.009$) and 10 g dose ($p<0.002$), where the mean serum potassium levels increased above 5 mEq/L (hyperkalemic range). Results continue to suggest ZS-9 is effective in the treatment of hyperkalemia and maintenance of normokalemia during the 12-day maintenance period, a trend we do not anticipate changing during longer periods of treatment given the clean safety profile of ZS-9 and excellent tolerability to date.

Relypsa also announced results of a subgroup analysis of heart failure patients from its two-part Phase III trial, although the patient population was not as broad as the patients included in the ZS Pharma study. The company noted a 1.06 mEq/L ($p<0.001$) reduction in potassium levels in patients with HF, which was described as similar to those without HF during the non-placebo-controlled Part A of the study (exhibit 2, page 3). During the placebo-controlled portion of the study, Part B, the difference between placebo (22 HF, 30 non-HF) and patiromer (27 HF, 28 non-HF) was 0.64 mEq/L ($p<0.001$). The company stated similar trends between patients in the heart failure subgroup who experienced recurrent hyperkalemia and the placebo group (8% compared with 52%, $p<0.001$) and noted a similar trend in non-heart-failure patients (23% compared with 66%, $p<0.001$), with the absolute difference ranging from 43% to 44% between active and placebo. Given the size of the ZS003 study (N=753) we believe the company's subgroup analyses is more robust, with 147 normokalemic heart failure patients, three times more patients than the 49 patients included in the patiromer subgroup analysis. We will not receive data from ZS-9 long-term use until 2015, when the extension portion of ZS004 and the long-term safety study ZS005 read out,

although normokalemic levels on average are achieved throughout the 12-day treatment period of ZS003 for the 5 g and 10 g doses, while placebo patients increased to above 5 mEq/L.

Exhibit 1

ZS Pharma Subgroup Analysis Study Design and Results

Study Design			Results
147 normokalemic HF patients on RAASi (after 48 h initiation phase, ZS-9 TID)			5g ZS-9: 4.7 mEq/L, (P < 0.009) 10g ZS-9: 4.9 mEq/L, (P < 0.002) placebo: >5 mEq/L
5g ZS-9 QD	10g ZS-9 QD	placebo	
12 day assessment of change in serum potassium			

Source: ZS Pharma reports

Exhibit 2

Relypsa Subgroup Analysis Study Design and Results

	Study Design				Results
PART A	243 patients with hyperkalemia				reduction of 1.06 mEq/L (P < 0.001) in HF patients
	102 HF +RAASi +patiromer		141 non-HF +RAASi +patiromer		
	4 week assessment of change in serum potassium				
PART B	Patients from Part A with baseline serum potassium ≥ 5.5 mEq/L at enrollment and controlled at week 4				recurrent hyperkalemia in HF patients: 8% (patiromer) vs. 52% (placebo), (P < 0.001) recurrent hyperkalemia in non-HF patients: 23% (patiromer) vs. 66% (placebo), (P <0.001) median change from Part B baseline in serum potassium was 0.64 mEq/L (P < 0.001) in HF patients
	49 HF and 58 non-HF met criteria for randomization into 2 groups (patiromer/placebo)				
	27 HF +patiromer	28 non-HF	22 HF +placebo	30 non-HF	
	4 week assessment of change in serum potassium (week 8 of total study)				

Source: Relypsa reports

Given consistent ZS003 results, we expect positive results from second Phase III Study, HARMONIZE, expected in late September/October. In the second quarter, ZS Pharma announced that it had completed enrollment of HARMONIZE (HyperkAlemia RandoMized interventiON multI-dose ZS-9 maintEnance clinical trial), the company's second Phase III study of ZS-9 for the indication of hyperkalemia. The study enrolled 258 patients with hyperkalemia at 42 sites, including patients with congestive heart failure (CHF), chronic kidney disease (CKD), and diabetes, including those on a variety of renin-angiotensin-aldosterone (RAAS) inhibitor therapies. The company expects top-line data from the trial to read out as early as the next several weeks, with full data to be presented at an upcoming medical conference. In addition, ZS Pharma is rolling HARMONIZE patients into an extension study, which is expected to eventually provide one year of open-label safety, tolerability, and efficacy data; however, we are unsure if one year or only six months of data will be included in the initial label for ZS-9. During the second quarter, the company also began enrolling ZS005, a 52-week open label safety and efficacy trial that should read out in 2015 and also supplement the company's regulatory filing. The company remains on track to file a NDA in the first half of 2015 and we continue to have a high conviction in the potential for success of ZS-9 in the long-term treatment of hyperkalemia and maintenance of normokalemia. We believe the product profile of ZS-9 continues to suggest a best-in-class product with a lower adverse effect profile than products currently on the market or under development given data to date and the underlying specificity ZS-9 holds in binding potassium.

The patiromer NDA submission is still on track for early in the fourth quarter, which we believe is approximately one to two quarters ahead of the NDA submission of ZS-9, which should occur in the first half of 2015. As shown in exhibit 3, the market capitalization of both ZS Pharma and Relypsa has been in the $750 million to $860 million range since August 25. And while investor interest now seems focused on handicapping the outcome of ZS004 (HARMONIZE) and the resulting stock

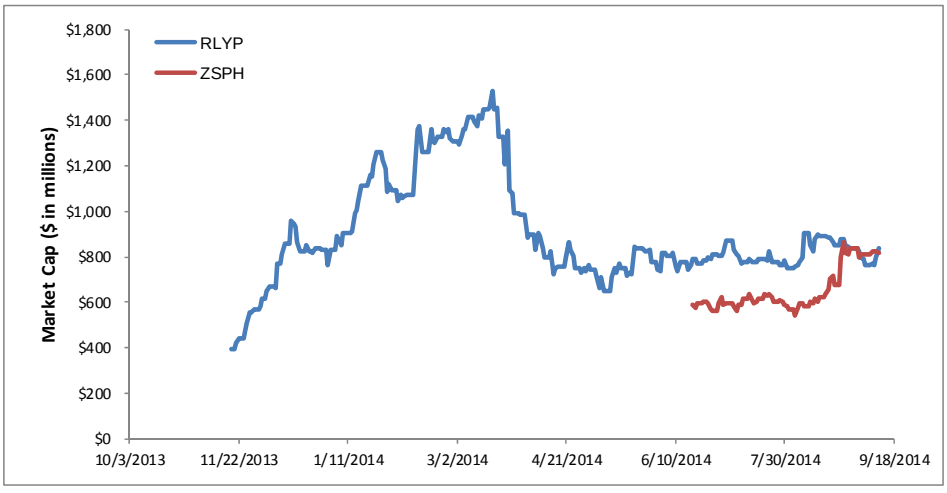
movement, we note that in the past Relypsa has reached a market cap of over $1.4 billion, suggesting significant upside is still possible if ZS-9 continues to look like a best-in-class agent.

The relative adverse event profile for patiromer seems to show a greater percentage of adverse events, and particularly GI events, in comparison to ZS-9. We believe these data show that ZS-9 has a best-in-class safety profile, which is in line with our view that the product is highly selective to binding potassium. In addition to a potential cleaner side effect profile, ZS Pharma enrolled a broader patient population, with the clinical trials recruiting patients with hyperkalemia regardless of etiology. We also believe ZS-9 as a once-a-day maintenance therapy likely has an improved profile over patiromer in the large chronic dosing market.

Although head-to-head studies of development compounds are rarely available and cross-trial comparison is always difficult because of different patient populations, we attempted to directionally compare the safety and efficacy profiles of ZS-9 and patiromer in exhibits 4 and 5, on page 5. In the early-stage study comparison, at the 48-hour period, ZS-9 patients (especially at doses above 2.5 grams three times per day, or TID) are in the normokalemic range after treatment, whereas patiromer patients are still above the range (though significantly reduced from baseline) for normal potassium concentration. In addition, in the comparison of data after two weeks of treatment, ZS-9 in the maintenance phase showed lower mean serum potassium concentration (4.71 mEq/L for 5 g QD, and 4.55 mEq/L for 10 g QD), while our best estimate for 14-day data for patiromer suggests end-values of 4.8 mEq/L for both the mild and moderate-to-severe hyperkalemia patients. We continue to believe that ZS-9 has a faster onset of action in comparison to patiromer.

Hyperkalemia is a life-threatening condition wherein elevated levels of potassium have been shown to increase the risk of ventricular fibrillation/cardiac arrest and death (Goyal et al. *JAMA* 2012). In total, we believe the hyperkalemia market exceeds 3 million patients in the United States alone, with few good treatment options. 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 and maintenance of normokalemia market. We view shares as our best near-term idea ahead of the readout of the HARMONIZE trial in late September/October.

Exhibit 3
ZS Pharma, Inc.
Comparison of ZSPH and RLYP Market Caps Since 2013



Source: FactSet, William Blair & Company, L.L.C.

Exhibit 4
ZS Pharma, Inc.
Safety Measures From ZS-9 and Patiromer (RLY5016)

	Induction Phase (48 h)		Maintenance Phase (2 weeks)	
Safety Measurement	Placebo	ZS-9	Placebo	ZS-9
All Adverse Events	10.8%	12.9%	24.5%	25.1%
GI Events	5.2%	3.5%	3.7%	5.5%

Safety Measurement	Placebo	RLY5016
All Adverse Events	31%	54%
GI Events	6%	21%

Sources: Pitt et al. Eur Heart J 2011, Company Reports, William Blair & Company, L.L.C.

Exhibit 5
ZS Pharma, Inc.
Change in Serum Potassium After Treatment With ZS-9 and Patiromer

Time Point	Patiromer	Dose	RLYP Study	ZS-9	Dose	ZSPH Study
48 hours	5.83 mEq/L -> 5.1 mEq/L	8.4g b.i.d.	Phase I Onset-of-Action	5.3 mEq/L -> 5 mEq/L	1.25g t.i.d.	ZS-003 Induction Phase
				5.3 mEq/L -> 4.84 mEq/L	2.5g t.i.d.	
				5.3 mEq/L -> 4.76 mEq/L	5g t.i.d.	
				5.3 mEq/L -> 4.57 mEq/L	10g t.i.d.	
2 weeks	Mild HK: ~5.2 mEq/L -> ~4.8 mEq/L Moderate/Severe HK ~5.6 mEq/L -> 4.8 mEq/L	10g t.i.d	RLY5016-205 (AMETHYST-DN)	5.3 mEq/L ->4.71 mEq/L	5g q.d.	ZS-003
				5.3 mEq/L -> 4.55 mEq/L	10g q.i.d.	Maint. Phase
4 weeks	Mild HK: ~5.1 mEq/L -> ~4.65 mEq/L Moderate/Severe HK: ~5.8 mEq/L -> 4.5 mEq/L	Mild: 8.4 q.d. Mod/Sev HK: 8.4g b.i.d.	Phase III	Study Results in Q4 2014		ZS-004
52 weeks	Mild HK: ~5.2 mEq/L -> ~4.6 mEq/L Moderate/Severe HK: ~5.65 mEq/L -> ~4.6 mEq/L	10-40g q.d.	RLY5016-205 (AMETHYST-DN)	Study Initiated in Q2 2014		ZS-005

Sources: ZS Pharma and Relypsa company reports

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 (exhibit 6). 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 Pharma of $1.17 billion by penetrating 10% to 13% of the available patient populations within select markets.

Exhibit 6
ZS Pharma, Inc.
Sum of the Parts Valuation

	Peak Sales	Discount Rate	Probability of Success	Peak Sales	Value Per Share
ZS-9	$1,170	11%	75%	2021	$ 72.40
Cash Per Share					$ 4.71
NPV of Future Losses Per Share					$ (2.41)
NPV Value					$ 1,807,728
NPV Value Per Share					$ 74.70

Source: William Blair & Company L.L.C. estimates
For per share numbers we use fully diluted share count of 24.2 million

Risks

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

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.

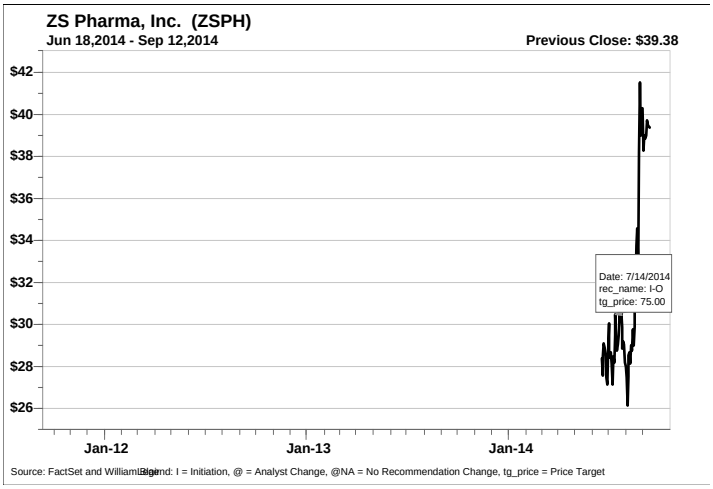
Additional information is available upon request.

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: 17,172.68
S&P 500: 1,994.29
NASDAQ: 4,527.69



Current Rating Distribution (as of 08/31/14)

Coverage Universe	Percent	Inv. Banking Relationships*	Percent
Outperform (Buy)	66	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.