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Therapeutics

Second Quarter 2015 Catalyst Watch: AAVL, BMRN, EGRX, PETX, RVNC, SAGE, SRPT, ZSPH

- In this note, we summarize clinical and regulatory stock-moving events of selected companies in our therapeutics coverage universe during the second quarter of 2015.

- The second quarter should hold several meaningful clinical catalysts within our coverage. Most notably is Avalanche Biotechnologies Phase 2a data for AVA-101, which is set to read out midyear. We anticipate these results will have a significant impact on the stock price with the majority of focus on visual acuity scores and reduction in Lucentis rescue use, despite the Phase IIa trial primarily being focused on safety and tolerability. Given the disruptive potential of AVA-101 in the $6 billion wet-AMD market, we expect the stock to have significant upside (over 75%-100%) if Phase II results are in line with Phase I results, which were an average of 0.33 Lucentis rescue injections per year and 6- to 8-letter improvement over baseline, depending on the dosage. The next major clinical event in our coverage is BioMarin Pharmaceutical's top-line data readout of BMN-111 in achondroplasia. Lastly, we expect ZS Pharma to report long-term data from its extension study and its long-term safety trial for ZS-9 toward the end of the quarter, which will allow for investors to make significant comparisons to competitor Relypsa's (RLYP $37.56) patiromer 52-week data-set (albeit in different populations) and sets the stage for the regulatory review over the next year.

- On the regulatory front, the most near-term catalyst will be Eagle Pharmaceuticals' NDA potential acceptance for EP-3102 on April 15, which will include a decision on Priority Review. As we have stated in earlier notes, we have confidence in the potential for Priority Review due to the FDA's recent MedWatch warning on Treanda due to a chemical in the drug that interacts with delivery devices that is not contained in EP-3102. Sarepta Therapeutics will be submitting its NDA in mid-2015 as it looks to meet guidance amidst several management changes and setbacks that have occurred at the company over the past 12 months.

- We expect M&A to remain a theme in the second quarter with large-cap and midcap companies seeking to add innovative pipeline assets. In our coverage universe, we anticipate Shire plc (SHPG $247.51; Outperform) to be active on the business development front with potential takeout targets including PTC Therapeutics (PTCT $71.12), BioMarin (BMRN $122.14), and Amicus Therapeutics (FOLD $11.90) all looking to advance the company's goal of becoming the leader in the rare disease space. In addition, we expect Endo International (ENDP $93.43; Market Perform) to be active on the M&A front as well with acquisitions to enhance its branded and generics portfolios after withdrawing its bid for Salix. Companies we see as good strategic fits for Endo include BioDelivery Sciences (BDSI$9.64; Outperform), Insys Therapeutics (INSY $59.50), Impax Laboratories (IPXL $50.09), Pacira Pharmaceuticals (PCRX $89.33), and Akorn (AKRX $51.36; Outperform).

Avalanche Biotechnologies, Inc.
AAVL (NASDAQ) $39.21
Stock Rating: **Outperform**
Company Profile: **Aggressive Growth**
Price Target: $53.00

BioMarin Pharmaceutical Inc.
BMRN (NASDAQ) $122.14
Stock Rating: **Outperform**
Company Profile: **Aggressive Growth**
Price Target: $104.00

Eagle Pharmaceuticals, Inc.
BMRN (NASDAQ) $49.31
Stock Rating: **Outperform**
Company Profile: **Aggressive Growth**
Price Target: $67.00

Aratana Therapeutics, Inc.
PETX (NASDAQ) $16.05
Stock Rating: **Outperform**
Company Profile: **Aggressive Growth**

Revance Therapeutics, Inc.
RVNC (NASDAQ) $21.26
Stock Rating: **Outperform**
Company Profile: **Aggressive Growth**
Price Target: $35.00

Sage Therapeutics, Inc.
SAGE (NASDAQ) $52.25
Stock Rating: **Outperform**
Company Profile: **Aggressive Growth**
Price Target: $75.00

Sarepta Therapeutics, Inc.
SRPT (NASDAQ) $13.68
Stock Rating: **Outperform**
Company Profile: **Aggressive Growth**
Price Target: $34.00

ZS Pharma, Inc.
ZSPH (NASDAQ) $43.28
Stock Rating: **Outperform**
Company Profile: **Aggressive Growth**
Price Target: $75.00

Additional Details:

Aratana Therapeutics
On its fourth-quarter earnings call, the company announced a delay in the readout of its pivotal trial with AT-002 for the indication of inappetence in dogs from the first quarter to the second quarter. In addition, the AT-003 pivotal study for the indication of post-surgical pain in dogs is expected to readout in midyear. Although there is a slight delay in the clinical readouts, we believe the company is on pace to receive FDA approval for AT-001, AT-002, and AT-003 in 2016 as previously guided and believe its strategy of performing positive pilot studies before moving into pivotal trials further de-risks the outcome.

Avalanche Biotechnologies
We consider the Phase IIa data readout to be the most significant event in our coverage universe in the second quarter (company has guided to mid-2015, most likely in June). Although the trial is primarily a safety and tolerability study, most investors will be focused on early signs of efficacy including any improvements over baseline for visual acuity and need for Lucentis rescue injections.

Under the current standard of care and label instructions, the patient would need about 6 to 12 injections per year. Many studies and real-world treatment regimens use an as-needed therapy, which has been shown to be roughly three to six intravitreal injections per year, versus AVA-101's value proposition of a single injection. While we believe OCT and visual acuity benefits are possible in the upcoming data set, we still believe shares would react favorably under several scenarios including an overall reduction in Lucentis rescue therapy to two doses on average (0.33 in Phase I), a subgroup of hyper-responders (given the large market), and a maintenance or improvement of vision scores. In addition, we would see efficacy signals in the Phase IIa as a significant proof of concept given the more "real-world" patient enrollment and the reproducibility of Phase IIa results in Phase IIb and Phase III trials for previous anti-VEGF clinical programs.

The baseline characteristics of patients in the Phase IIa and Phase I study are shown in exhibit 1. When comparing the baseline characteristics from the first two studies, patients had a much higher BCVA score in the Phase IIa study than the Phase I study, which reflects ophthalmologists increasing comfort in allowing patients with better vision to be enrolled in the study and not restricting access to patients with severe disease. There was one patient who did not achieve an increase in visual acuity score in the Phase I trial, which the company attributed to significant fibrosis and scarring at baseline. We believe the "healthier" population enrolled in the Phase IIa trial better represents the patients that achieved a visual acuity improvement in the Phase I trial. We would expect shares to hold significant upside if results suggest significant reductions in Lucentis rescue therapies as investors gain confidence in the Ocular BioFactory platform technology and management's ability to execute on its deep clinical pipeline, which includes AVA-201 for preventative wet-AMD therapy, AVA-311 for X-linked juvenile retinoschisis (XLRS) with co-partner Regeneron Pharmaceuticals (REGN $456.98), and newly added AVA-322 and 323 for color blindness.

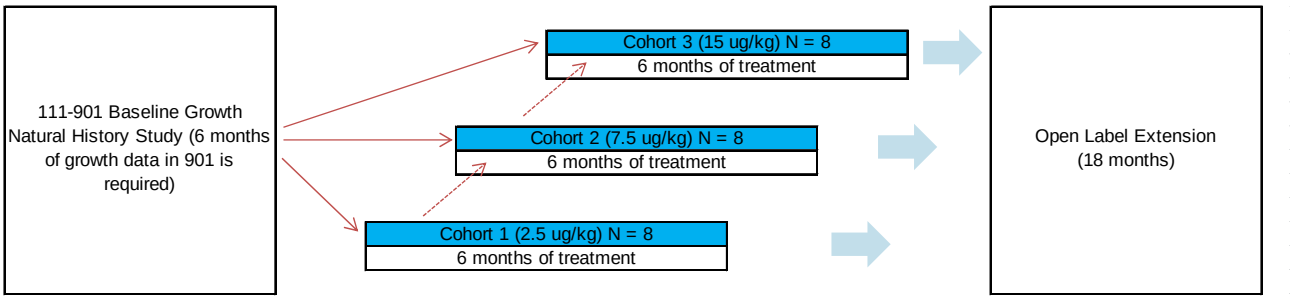
Exhibit 1
Phase IIa Baseline Characteristics Compared to Phase I

	Phase I	Phase IIa
Age (years)	79 (71-86)	79.5 (62-95)
Baseline BCVA (ETDRS letters)	36.5 (28-56)	63 (35-78)
Baseline center point thickness (μm)	549 (193-1094)	332.5 (179-816)
Number treatment naïve (n/N)	0/8	4/32
Previous anti-VEGF injections (for non-naïve)	11.5 (1-29)	10.5 (1-25)
Time since diagnosis (months)	49.2 (2-65)	16.2 (0-85)

all values median (range)
Source: Company reports

BioMarin Pharmaceutical
BMN 111 is currently in a phase II, open-label, sequential, cohort, dose-escalation study in children with achondroplasia that is set to read out data on the first three cohorts in the second quarter of 2015 (exhibit 2). The primary endpoint of the study is the safety and tolerability with a six-month run-in period to obtain baseline growth velocities of each patient. The secondary endpoints are the change from baseline in annual growth velocity, growth parameters, and body proportions following daily subcutaneous injections of BMN 111. Subjects who have completed a six-month natural history study are placed into three cohort groups with doses of 2.5 μg/kg, 7.5 μg/kg, and 15 μg/kg, and after completion of the cohort dosing, have the option to continue with BMN111 in an open-label extension study (which is currently guided for 18 months). We believe that the study has a high probability of success due to the literature on the development of achondroplasia and BMN 111's mechanism of action through the MAPK pathway.

Exhibit 2
BMN111-202 Study Design



Source: BioMarin company reports

At its R&D analyst event last year, the company discussed the importance of growth velocity and proportional growth from the company's natural history study. The baseline characteristics for Study 901 look to be in line with the natural history study; achondroplasia patients enrolled in the study are under the fifth percentile in height and clustered between five and seven years of age. The growth velocity of these patients will vary, with a 50% improvement placing the younger children in the study on the normal growth curve, while an 80% improvement may be more important for the older children who may need to catch up after several years of low growth. Dr. Cathleen Raggio, an orthopedic surgeon from the Hospital of Special Surgery in New York, also noted that there are several spurts for spinal column growth between the ages of 0-2, 7-8, and puberty, and increases in spinal column size would be significantly meaningful for these patients, likely preventing multiple future surgeries.

We see BMN-111 as the next most significant pipeline asset (along with drisapersen) for the company after the approval of Vimizim and expect results from the first three cohorts to guide future clinical development of this compound, which has a potential market of 250,000 patients worldwide. To put BMN-111 in perspective, most successful lysosomal storage disease therapies address populations under 10,000 patients with the recently launched VIMZIM addressing a potential market of 3,000 patients worldwide. As our current NPV-derived price target does not include any value for BMN-111, and the product (along with drisapersen) represents one of the largest pipeline assets for the company, we will maintain our Outperform rating and adjust our NPV following data results.

Eagle Pharmaceuticals
The PDUFA date may be moved up to August 15 from December 15 if EP-3102 is awarded Priority Review from the agency, which we will be announced in the near term (April 15). We have increased confidence in the product receiving the expedited review, which would provide upside to our current estimates. We assume that if Priority Review is received, the launch would move up a quarter to the fourth quarter of 2015 from the first quarter of 2016 and potential sales milestones could be met earlier, which would increase the royalty rate to above 20% in 2016, as we would expect a relatively hard switch to EP-3102 and we believe royalties start at 20% and escalate from there.

In our current estimates, we assume a launch of EP-3102 in early 2016 pending a standard 10-month review period and that Teva will transfer roughly 75% of the Treanda market onto EP-3102, which should be conservative given an over-90% conversion of Teva's lyophilized formulation to its liquid formulation. We continue to believe the rapid infusion product has the potential to be best-in-class addition to the Treanda franchise for partner Teva (TEVA $66.02) with a 50 ml bag reducing the volume infused into the patient by 90%. This reduction in volume is a significant safety differentiation for the product given the high rate of patients with compromised kidney function in the hematologic markets.

Aside from events related to EP-3102, Eagle anticipates filing its RTU bivalirudin (EP-6101) 505(b)2 NDA in the second quarter. However, the major event for this product opportunity is likely the outcome of the current litigation between The Medicines Company (MDCO $29.30) and Hospira (HSP $87.64) after the brand manufacturer (MDCO) appealed a Federal Court decision that Hospira's generic bivalirudin did not infringe on U.S. No. '727 and U.S. No. '343 (expiration in 2028), which were upheld in the same decision. The results from this appeal are expected in the June/July time frame and will likely influence whether the brand market will remain intact for several more years, resulting in a more attractive potential for Eagle's 505(b)2, or whether Eagle will enter the market with generic competition.

We reiterate our Outperform rating on Eagle as company management has executed on all of its stated goals since becoming a public company in 2014, and despite the stocks strong performance to date, we remain buyers ahead of a catalyst-rich next 12 months, which will mainly include the approval of EP-3102. A valuation based on a below-peer-group multiple of 15 times our

new 2016 estimate of $4.44 brings us to a $67 share price as the company transforms into a profitable specialty pharmaceuticals company with significant cash flow pending the approval of EP-3102. However, with an approval in August and launch in September, we believe 2016 EPS could exceed $6.00, which would suggest a $90 stock if applying a 15-multiple.

Revance Therapeutics
During the second quarter of 2015, we expect data from the company's open-label proof of concept for RT001, which will use product from an improved manufacturing process. Pending position results from this study, Revance will initiate a pivotal Phase III program in lateral canthal lines (crow's feet). By mid-2015 Revance management will also initiate a Phase II study of RT001 for the treatment of hyperhidrosis, which should report out preliminary results by the end of the year while a Phase II study in movement disorders will also be initiated and report out interim data in a similar time frame.

In general, we view Revance as an attractive name for the second half of 2015 as we will probably receive meaningful updates from four clinical trials during the second half of the year in four different indications and we view shares as holding a significant risk/reward profile from current levels.

Sage Therapeutics
The company recently reported on its end of Phase II meeting with the FDA that included a clinical trial design for a Phase III trial for SAGE-547. Sage also has a Phase I/II trial ongoing in which the primary endpoint of safety and tolerability was achieved in all patients at the most recent examination of data. Of the 17 evaluable patients for efficacy, 71% of patients (12 of 17) achieved the efficacy endpoint of weaning off general anesthetic, while SAGE-547 was being administered and being weaned off SAGE-547 without recurrence of SRSE. In addition to the clinical trial cases, SAGE-547 has received emergency-use investigational new drug (IND) status for 10 patient cases. Of the nine evaluable emergency-use cases, 78% (seven of nine) of the patients were able to wean off general anesthetic and SAGE-547 with no SRSE and duration of effect greater than, or equal to, 24 hours. The trial is ongoing with the company having received a protocol amendment from the FDA for higher dosing and to treat patients as young as two years old. Results are expected to be announced at the Antiepileptic Drug and Device Trials XIII Conference taking place May 13-15 as well as at the American Academy of Neurology Meeting—Emerging Science Session on Wednesday April 22.

Beyond SRSE, the company has two follow-on indications for SAGE-547 (essential tremor and severe postpartum depression) that are being tested in exploratory trials, which should readout in mid-2015 as well as two pipeline compounds, SAGE-689 and SAGE-217, that are guided to enter the clinic in late 2015

Sarepta Therapeutics
Sarepta's eteplirsen NDA submission is the near-term catalyst for the company, which is being guided toward midyear. However, the pre-NDA meeting will influence this timing. Previously, the FDA had requested three months of safety data from at least 12 to 24 newly exposed patients at the time of NDA submission, available data (even if under three months, again safety) from other patients enrolled in new eteplirsen studies (study 301, 203, and 204), additional data from later time points and newly enrolled patients from the company at the 120-day safety update as well as MRI data from an ongoing independent NIH sponsored study with an academic group, and patient-level natural history data. While there is a potential for a setback in the filing of the company's NDA given several moving parts including progression of patients at week 168 and the outcome of the fourth biopsy under that scenario, the company should be able to refile with the FDA with data from the company's confirmatory study, which should produce data during the second half of 2016.

We continue to rate Sarepta shares Outperform as we believe the company has a strong risk/reward profile in 2015 given a rocky 2014 due to the renewed focus on completing their NDA submission to the FDA. However, given the back and forth between the FDA and the company to date, we believe shares will likely continue to be volatile, and if the agency does not accept the company's eteplirsen NDA, we will likely have to wait until additional data is available from the company's ongoing and large Study 301 (enrolling 60 to 80 patients) before another filing occurs.

ZS Pharma
The next meaningful catalysts for ZS Pharma will likely be the filing of the ZS-9 NDA and long-term safety study data, both of which we believe may occur in the second quarter. In total, the acute and chronic hyperkalemia market exceeds 3 million patients in the United States by our estimates 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 believe that long-term safety data could cement that profile.

We recently attended the National Kidney Foundation's Spring Clinical Meeting in Dallas, Texas, and 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 3, we highlight some characteristics in 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 roughly 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, which may serve as a differentiator with both potentially in the market by the end of 2016.

We continue to rate ZS Pharma shares 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 that 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.

Exhibit 3
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 4
Second Quarter Catalyst Events in Therapeutics Coverage

Type	Company	Ticker	Rating	Current Price	Market Cap ($ in millions)	Event
Clinical	Aratana Therapeutics	PETX	O	$16.25	$567	AT002 Pivotal Trial Readout
	Avalanche Biotechnologies	AAVL	O	$40.69	$1,026	Phase 2 data for AVA-101 (mid-2015)
	BioMarin Pharmaceutical	BMRN	O	$122.20	$19,446	Phase I/II data BMN-111 in Achondroplasia Data (2Q)
	Revance Therapeutics	RVNC	O	$20.97	$502	RT001 manufacturing study and Phase III initiation
	Sage Therapeutics	SAGE	O	$51.41	$1,327	Phase I/II trial data readout May (13th-15th)
	ZS Pharma	ZSPH	O	$43.00	$1,071	Long-term data for ZS-9 (mid-2015)
	Eagle Pharmaceuticals	EGRX	O	$49.31	$751	NDA Acceptance and Potential Priority Review (April 15th)
Regulatory	ZS Pharma	ZSPH	O	$43.00	$1,071	ZS-9 NDA Submission (2Q)
	Sarepta Therapeutics	SRPT	O	$13.85	$572	Eteplirsen NDA submission (mid-2015)

Sources: Company reports, FactSet, William Blair & Company, L.L.C.

Exhibit 5
First Quarter Catalyst Events in Therapeutics Coverage

Type	Company	Ticker	Rating	Price on Publication	Market Cap ($ in millions)	Current Price	Market Cap ($ in millions)	Event	Difference	%
Commercial	Akorn, Inc.	AKRX	O	$41.98	$4,527	$52.74	$5,438	Aging ANDA pipeline updates including 20 products filed for over 36 months (4 tentative approvals)	$10.76	26%
	Adamas Pharmaceuticals	ADMS	O	$16.60	$284	$17.94	$311	Initiation of Clincal Trial in New Indication for ADS-5102	$1.34	8%
Clinical	Aratana Therapeutics	PETX	O	$17.13	$594	$16.25	$567	AT002 Pivotal Trial Readout	-$0.88	-5%
	BioDelivery Sciences International	BDSI	O	$12.02	$616	$9.50	$519	Clonidine Topical Gel Phase III Topline Readout	-$2.52	-21%
	Eagle Pharmaceuticals	EGRX	O	$16.73	$235	$49.31	$751	Update on meeting with FDA on 10 min bendamustine product	$32.58	195%
Regulatory	Shire plc	SHPG	O	$216.98	$42,514	$248.77	$47,815	PDUFA Dates for Natpara (January 24, 2015) and Vyvanse for Binge Eating Disorder (February 1, 2015)	$31.79	15%
	Zogenix	ZGNX	M	$1.33	$204	$1.49	$225	PDUFA Date for sNDA of abuse-deterrent formulation of Zohydro ER (January 30, 2015)	$0.16	12%

Sources: Company reports, FactSet, William Blair & Company, L.L.C.

IMPORTANT DISCLOSURES

Additional information is available upon request.

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DOW JONES: 18,057.65
S&P 500: 2,102.06
NASDAQ: 4,995.98

Current Rating Distribution (as of 03/31/15)

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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