November 20, 2017

OUTPERFORM

Reason for report:

PROPRIETARY INSIGHTS

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LEERINK

VERTEX PHARMACEUTICALS INCORPORATED

GLPG Establishes PoC for CFTR Corrector but No Tezacaftor

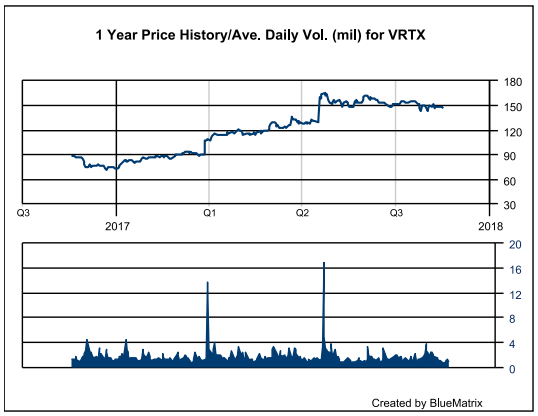
• **Bottom Line:** Yesterday Galapagos Pharmaceuticals reported the first proof of concept (PoC) from a non-Vertex cystic fibrosis (CF) small molecule CFTR corrector, with data for its first-generation CFTR corrector GLPG2222 in patients on stable Kalydeco. These results in F508del/gating mutation CF patients are a less optimal data set for interpretation and comparison to Vertex's molecules given the failure of TEZ/IVA in phase III for this well-controlled population, but the small efficacy signal and clean safety profile suggest Galapagos may have one piece of its triple-combination puzzle. However, the lung function results are inferior to Vertex's TEZ/IVA, albeit in a small patient population, and the question still remains if three of Galapagos' proprietary medicines can be combined safely or can match Vertex's efficacy. There is a vast amount of work in front of GLPG and its potential partner AbbVie (ABBV, OP) to challenge Vertex in this category. These results do not yet compel us to alter our CF market model, which currently forecasts competition from Galapagos with an ultimate probability of success of 25%. We maintain our VRTX OP rating and $179 price target.

• **While the GLPG2222 Results Demonstrate Activity, Galapagos' Development Timeline Remains Lengthy and Uncertain in the US.** We continue to believe the late to market development strategy for Galapagos places the company and its partner AbbVie at a minimum 2 years behind Vertex for a triple combination that can treat the majority of CF patients (see our note here: "VRTX – Competition from GLPG's Program is 2 Years Behind, With Many Hurdles"). Galapagos announced that GLPG2222 will move forward into two proprietary triple-combo phase I studies in healthy volunteers, but these trials are only in Europe, and the US development strategy remains slow and unclear (see our note here: "GLPG Has Great Molecules, But Does it Have a Drug (in the US)?").

• **Phase II GLPG2222 Trial in F508del/Gating Population Is Inferior to Failed Phase III TEZ/IVA Study.** The ALBATROSS trial was a phase II study conducted in Europe and Australia that recruited 37 heterozygous F508del/gating mutation adult CF patients in 5 months. Much like Vertex's TEZ/IVA gating study, all patients entered the study period on a stable dose of Kalydeco monotherapy, and were randomized to receive GLPG2222 150mg QD (n=15), 300mg QD (n=14), or placebo (n=7) for 4 weeks (maintaining their background treatment with Kalydeco). These patients were likely well-controlled on Kalydeco based on the proven efficacy in gating mutation patients, and recall that Vertex's TEZ/IVA failed to show a statistically significant benefit in its phase III trial for this population despite showing an additive benefit in phase II. The primary endpoint of ALBATROSS was safety and tolerability, and the key secondary endpoints to determine the drug's efficacy were change in baseline from sweat chloride and change in lung function measured by forced expiratory volume in one second (FEV1). The baseline mean

Key Stats:	**(NASDAQ: VRTX)**
Sector:	**Biotechnology**
S&P 500 Health Care Index:	**938.86**
Price :	**$147.41**
Price Target:	$179.00
Methodology:	Avg. of 23.0x '21E EPS, 9.2x '22E revs. disc. to '18, and DCF at 9% WACC and 2% TG
52 Week High:	$167.86
52 Week Low:	$71.46
Shares Outstanding (mil):	256.0
Market Capitalization (mil):	37,737.0
Book Value/Share:	$3.63
Cash Per Share:	$6.63
Net Debt to Total Capital:	(194)%
Dividend (ann):	$0.00
Dividend Yield:	0.0%
Est LT EPS Growth:	55%
P/E to LT EPS Growth (FY18):	1.15

Completion: November 20, 2017, 6:27AM EDT.
Distribution: November 20, 2017, 6:27AM EDT.
Est LT EPS Growth: '17-'21E



Dec Yr	1Q	2Q	3Q	4Q	FY Rev	1Q	2Q	3Q	4Q	FY EPS	P/E
2016A	$397.2	$431.5	$413.5	$458.5	$1,700.7	$0.09	$0.24	$0.16	$0.35	$0.84	NM
2017E	$482.3A	$516.9A	$551.9A	$590.3	$2,141.3	$0.41A	$0.39A	$0.53A	$0.52	$1.85	79.7x
2018E	$610.6	$626.5	$636.1	$651.9	$2,525.2	$0.56	$0.55	$0.59	$0.64	$2.34	63.0x

Source: Company Information and Leerink Partners LLC Research
Revenues in millions.
EPS diluted, excluding options expense

FEV1 for patients at screening was 70%, which is higher than usual for most phase II TEZ/IVA trials that recruited patients between 55% and 65%.

• **GLPG2222 Efficacy Ekes by With Sweat Chloride Benefit Numerically Inferior to TEZ in Similar Population (see chart inside).** Galapagos reported that at week 4 GLPG2222 resulted in a statistically significant dose-dependent decrease in sweat chloride concentration of -6.0mmol/L and -3.8mmol/L in the 300mg and 150mg cohort, respectively, compared to an increase of +5.6mmol/L for placebo. In the scheme of the typical effect of such treatments, these changes are modest. The 300mg dose is comparable, but numerically inferior, to the phase II results of Vertex's tezacaftor in the same population, which produced a -7.0mmol/L decrease in sweat chloride. On lung function, the results for GLPG2222 were less favorable. There was no dose-dependent signal for FEV1 with the 150mg patients declining by an absolute -0.6%, which was almost equivalent to the placebo decline of -0.8%. Further, the beneficial +2.2% FEV1 increase for the GLPG2222 300mg cohort was not statistically significant and also below the tezacaftor improvement of a +4.6% absolute FEV1 increase. To us, these results indicate that GLPG2222 is unlikely to produce a meaningful lung function benefit for this population, and would likely fail in a similar manner as TEZ/IVA in a phase III irrespective of the potentiator used (Kalydeco or a proprietary Galapagos molecule). However, it does signal that the drug has some activity, at least at the 300mg dose, and trials of dual-combinations of '2222 with a proprietary potentiator in homozygous F508del patients are likely to succeed barring any safety, adverse event or drug-drug interaction liabilities of the combination with a Galapagos cystic fibrosis transmembrane conductance regulator (CFTR) potentiator.

• **GLPG2222 Apparently Passes Initial Safety Hurdle; Combinability With Proprietary Potentiator Still Unknown.** Full details of the safety and adverse event for this combination were not reported, but the top-line safety results are positive. Galapagos reported that GLPG2222 was well tolerated by patients on stable Kalydeco, and the adverse event profile was similar to a typical CF patient population. No serious adverse events were reported, and importantly no discontinuations occurred due to adverse events. The real test for Galapagos will be combining GLPG2222 with a proprietary GLPG potentiator and second-gen CFTR corrector. The craft of combining CF medicines has not been easy for Vertex, as evidenced by its stumbles with the toxicity profile of Orkambi and the multiple shots on goal still planned for its triple combination strategy. Even Vertex, with all its resources and experience, is preparing for the discontinuation of some of its molecules based on adverse events, tolerability or drug-drug interaction (DDI) issues. Until Galapagos can show it has comparable efficacy and adequate (placebo-like) safety and tolerability, we are hesitant to consider its program or portfolio as serious contenders to the CF treatment market currently dominated by Vertex.

INVESTMENT THESIS

Our price target for Vertex (VRTX) is $179 and we rate the stock Outperform. Our thesis is based on our expectation of continued capture of cystic fibrosis (CF) patient subpopulations by Vertex with its successive iterations of CF modulating oral combination medicines. We expect that Vertex's CF revenue line will grow steadily from ~$1.7bn in 2016 to ~$2.5bn by 2018E. Our probability of success for the triple combination is now 100% and our valuation accounts for our full expected value of the CF portfolio. While we consider competitors in our forecasts and valuation, we believe their development path and time to market are challenging, and Vertex is well positioned to partner with or acquire any that show promise. After flirting with profitability in the past, Vertex seems determined to maintain its recently recovered profitability and appears capable of growing its operating margin to ~27% by the end of 2017E and 30% by the end of 2018E and beyond. The company still aspires to discover and develop drugs in other categories, and large diversifying investments and associated expenses are a risk to our thesis and valuation. However, with the potential for sizable near-term growth, the stock offers strong valuation upside potential in the next 12-18 months.

Exhibit 1: GLPG2222 Versus Ivacaftor (With Background Kalydeco) in F508del/Gating

	Phase II w/Ivacaftor	Phase II	Phase II
	F508del/G551D ages 12+	F508del/G551D	F508del/G551D
	Tez/Iva (100mg qd / 150mg bid)	GLPG2222 (150mg qd) + Ivacaftor (150mg bid)	GLPG2222 (300mg qd) + Ivacaftor (150mg bid)
	n=14	n = 15	n = 14
Baseline percent predicted FEV1	59.1%	70.0%	
Mean absolute improvement in FEV1	4.6%	-0.6%	2.2%
Mean relative improvement in FEV1 (vs pbo)	7.3%	0.2%	3.0%
Mean absolute change in sweat chloride	-7.0 mmol/L	-3.8 mmol/L	-6.0 mmol/L
*measured at week 4			

Source: Pilewski et al., North American Conference of the Cystic Fibrosis Foundation 2014, Galapogos Company Press Release

VALUATION

Our price target for Vertex (VRTX) is based on a simple average of three approaches that we believe are a reasonable basis for valuing the stock today. These approaches are simple price to earnings multiples for high growth large cap biopharmaceutical companies; price to sales multiples for mid and large cap high growth biopharmaceutical companies, and discounted cash flow (DCF). Using a current average high growth large cap biopharma multiple of 2018 EPS (ALXN, REGN) of 22.2x, applied to our current 2021E EPS estimate for VRTX of $9.57, and discounted back 2 years at the company's 9% cost of equity, gives a value of $178 in one year. Using an average high growth large cap biotech price-to-revenue multiple of 2018E sales (REGN, ALXN, BMRN) of 8.1x, applied to our 2022E revenue estimate for VRTX (post-triple) of $6.3bn, and discounted back 3 years at the company's 9% cost of equity, gives a value in one year of $174. Lastly, our DCF valuation given a 9% WACC and a terminal cash flow growth rate of 2% gives a present value of $186. The average of these three methods is our current price target of $179.

RISKS TO VALUATION

The risks to our view, outlook, and valuation for Vertex include any major change in the price or reimbursement coverage, labelling, or competitive position for Kalydeco and Orkambi, the company's main products today. The other major risk is any disappointment, delay, or failure in the company's development and regulatory filings of its second first generation CF corrector, tezacaftor, or of the company's much-anticipated dual corrector/potentiator triple combination program. Other risks include accelerated or successful development of alternative modulators of CFTR, or alternative approaches to treating CF, such as gene therapy. Finally, the company has a history of spending much of its potential earnings, and expensive diversifying acquisitions could undermine the future expected value of the company's CF portfolio. Opportunities for better-than expected performance include realization of significant revenue from the company's current CF dual combination in markets outside the US, as well as accelerated clinical development of a viable triple combination regimen.

Leerink Vertex Revenue Forecast ($ in millions)	**2016A**	**1Q17A**	**2Q17A**	**3Q17A**	**4Q17E**	**2017E**	**1Q18E**	**2Q18E**	**3Q18E**	**4Q18E**	**2018E**	**2019E**	**2020E**	**2021E**	**2022E**
Non-Product Sales Revenue															
Non-Product Sales Revenue	18	2	3	3	4	11	1	3	3	4	10	9	9	9	9
Product Sales (all POS adjusted)															
Kalydeco monotherapy	704	186	190	213	232	820	222	225	230	233	909	854	738	643	633
Orkambi (Vx809/Kalydeco)	979	295	324	336	355	1,310	367	359	344	336	1,406	1,424	1,176	808	613
Combo Vx661/Kalydeco (2017 approval/2018 full year sales)	-	-	-	-	-	-	20	40	60	80	200	1,160	2,365	2,395	2,070
Triple Combination of Kalydeco, Vx661, second corrector (2020 full year s	-	-	-	-	-	-	-	-	-	-	-	-	200	1,850	3,010
Total Product Sales (booked by VRTX)	1,683	481	514	549	586	2,130	609	624	634	648	2,515	3,438	4,479	5,696	6,325
Total Revenues (Non-GAAP)	1,701	482	517	551.9	590.3	2,141	611	627	636.1	651.9	2,525	3,448	4,488	5,705	6,334
ANNUAL GROWTH															
Non-Product Sales Revenue															
Non-Product Sales Revenue	-7%	-20%	-18%	-16%	-14%	-38%	-13%	-11%	-10%	-9%	-10%	-6%	-4%	-2%	-2%
Product Sales (all POS adjusted)															
Kalydeco monotherapy	11%	9%	5%	21%	31%	17%	19%	18%	8%	0%	11%	-6%	-14%	-13%	-2%
Orkambi	179%	32%	32%	44%	28%	34%	25%	11%	2%	-5%	7%	1%	-17%	-31%	-24%
Combo Vx661/Kalydeco	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	480%	104%	1%	-14%
Triple Combination	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	63%
Total Product Sales (booked by VRTX)	70%	22%	21%	34%	29%	27%	27%	21%	15%	11%	18%	37%	30%	27%	11%
Total Revenues (Non-GAAP)	69%	21%	20%	33%	29%	26%	27%	21%	15%	10%	18%	37%	30%	27%	11%

Source: Leerink Partners Research and Company Filings

Leerink Vertex Income Statement Model															
($ in millions)	**2016A**	**1Q17A**	**2Q17A**	**3Q17A**	**4Q17E**	**2017E**	**1Q18E**	**2Q18E**	**3Q18E**	**4Q18E**	**2018E**	**2019E**	**2020E**	**2021E**	**2022E**
Revenues:															
Product sales (direct product sales by Vertex)	$1,683	$481	$514	$549	$586	$2,130	$609	$624	$634	$648	$2,515	$3,438	$4,479	$5,696	$6,325
Other revenue (includes royalties, milestones)	$18	$2	$3	$3	$4	$11	$1	$3	$3	$4	$10	$9	$9	$9	$9
Total revenues	**$1,701**	**$482**	**$517**	**$552**	**$590**	**$2,141**	**$611**	**$627**	**$636**	**$652**	**$2,525**	**$3,448**	**$4,488**	**$5,705**	**$6,334**
Expenses:															
Cost of sales	$210	$47	$71	$73	$77	$268	$61	$81	$82	$84	$309	$421	$548	$660	$692
R&D	$861	$227	$240	$243	$255	$965	$281	$282	$280	$280	$1,123	$1,183	$1,141	$1,177	$1,143
SG&A	$344	$86	$93	$91	$97	$367	$97	$95	$94	$93	$378	$446	$517	$609	$645
Profit share	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
Other expenses	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
Total expenses	$1,415	$360	$405	$407	$429	$1,600	$438	$458	$456	$457	$1,810	$2,050	$2,206	$2,446	$2,480
Operating income (EBIT)	$285	$122	$112	$145	$161	$541	$172	$168	$180	$194	$715	$1,397	$2,282	$3,259	$3,854
Nonoperating income (interest), net	($77)	($17)	($17)	($15)	($17)	($66)	($17)	($17)	($16)	($16)	($66)	($57)	($43)	($24)	($0)
Pre-tax income	$208	$105	$95	$131	$144	$475	$155	$151	$164	$179	$650	$1,340	$2,239	$3,235	$3,854
Tax (incl. NOL adjustment)	($0)	$4	($4)	($6)	$10	$4	$11	$11	$11	$13	$45	$94	$233	$647	$771
Pro Forma Earnings (Excluding Options Expense):															
Net income	**$208**	**$101**	**$99**	**$136**	**$134**	**$471**	**$144**	**$141**	**$153**	**$166**	**$604**	**$1,246**	**$2,006**	**$2,588**	**$3,083**
Earnings per share (basic):	**$0.85**	**$0.41**	**$0.40**	**$0.54**	**$0.53**	**$0.00**	**$0.57**	**$0.56**	**$0.60**	**$0.65**	**$2.38**	**$4.82**	**$7.65**	**$9.73**	**$11.44**
Earnings per share (diluted, *excluding option expense*)	**$0.84**	**$0.41**	**$0.39**	**$0.53**	**$0.52**	**$1.85**	**$0.56**	**$0.55**	**$0.59**	**$0.64**	**$2.34**	**$4.74**	**$7.52**	**$9.57**	**$11.26**
Weighted ave. shares (basic):	245	246	248	250	251	249	253	254	255	256	254	258	262	266	269
Weighted ave. shares (diluted):	247	249	252	256	257	254	257	258	259	260	258	263	267	270	274
MARGIN ANALYSIS:															
Gross margin (1-COGS/total revenue)	88%	90%	86%	87%	87%	87%	90%	87%	87%	87%	88%	88%	88%	88%	89%
R&D to total revenue	51%	47%	47%	44%	48%	45%	46%	45%	44%	43%	44%	34%	25%	21%	18%
SG&A to total revenue	20%	18%	18%	16%	16%	17%	16%	15%	15%	14%	15%	13%	12%	11%	10%
Operating margin (EBIT/total revenue)	17%	25%	22%	26%	27%	25%	28%	27%	28%	30%	28%	41%	51%	57%	61%
Effective tax rate	0%	3%	-4%	-4%	7%	1%	7%	7%	7%	7%	7%	7%	10%	20%	20%
Net margin (net income/total revenue)	12%	21%	19%	25%	23%	22%	24%	22%	24%	25%	24%	36%	45%	45%	49%
ANNUAL GROWTH															
Total revenues	69%	21%	20%	33%	29%	26%	27%	21%	15%	10%	18%	37%	30%	27%	11%
EPS (diluted)	-176%	343%	67%	229%	48%	120%	38%	39%	11%	22%	26%	103%	59%	27%	18%

Source: Leerink Partners Research and Company Filings

Analysis of Stock Price and Leerink Target for Vertex Pharmaceuticals

Method 1 - Large-Cap Healthcare 2018 EPS Multiple on 2021 LP VRTX Normalized Earnings	
Current Average High Growth **Large Cap** High Growth Biopharma Multiple of 2018 EPS (ALXN, REGN)	22.2x
Leerink EPS for VRTX (2021)	$9.57
Implied Price for 2020 on 2021 EPS (using current consensus high growth large cap multiple of 2017	**$212**
Cost of Equity	**9.0%**
Number of Periods (2020-2018)	2
Implied One Year Target Price by approach	**$178**
Method 2 - Discounted Future Value of Normalized Revenue Using Mid and Large Cap Biotech Comparables	
Average Growth Large Cap and Mid Cap Biotech Price-to-Revenue Multiple of 2018 Sales (REGN, ALXN, BMRN)	8.1x
Vertex 2022 Recurring Revenue (+triple) ($mm)	$6,334
Implied Vertex Enterprise Value in 2021 on 2022 Sales Est ($mm)	$51,571
Est. Net Cash in 2021	$6,945
Implied Vertex Equity Value in 2021 ($mm)	$58,516
Cost of Equity	9.0%
Number of Periods (2021-2018)	3
Implied Vertex Value in 2018 ($mm)	$45,304
Anticipated Share Count End 2018 (mm)	260
Implied One Year Target Price by approach	**$174**
Method 3 - DCF Based on Current Products and POS Adjusted Outlook for CF Franchise Only Using 9% WACC and 2% terminal cash flow growth rate	
Present Value of Late Stage and Marketed Product Cash Flows	$46,689
Cash Net of Debt end 2017	$1,583
Total Value	$48,271
Shares O/S End 2018	260
Implied One Year Target Price	**$186**
Average of Methods	**$179**
Leerink Target Price	**$179**

Source: Leerink Partners Research and Company Filings, Factset

Disclosures Appendix

Analyst Certification

I, Geoffrey C. Porges, MBBS, certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

Valuation

Our price target for Vertex (VRTX) is based on a simple average of three approaches that we believe are a reasonable basis for valuing the stock today. These approaches are simple price to earnings multiples for high growth large cap biopharmaceutical companies; price to sales multiples for mid and large cap high growth biopharmaceutical companies, and discounted cash flow (DCF). Using a current average high growth large cap biopharma multiple of 2018 EPS (ALXN, REGN) of 22.2x, applied to our current 2021E EPS estimate for VRTX of $9.57, and discounted back 2 years at the company's 9% cost of equity, gives a value of $178 in one year. Using an average high growth large cap biotech price-to-revenue multiple of 2018E sales (REGN, ALXN, BMRN) of 8.1x, applied to our 2022E revenue estimate for VRTX (post-triple) of $6.3bn, and discounted back 3 years at the company's 9% cost of equity, gives a value in one year of $174. Lastly, our DCF valuation given a 9% WACC and a terminal cash flow growth rate of 2% gives a present value of $186. The average of these three methods is our current price target of $179.

Risks to Valuation

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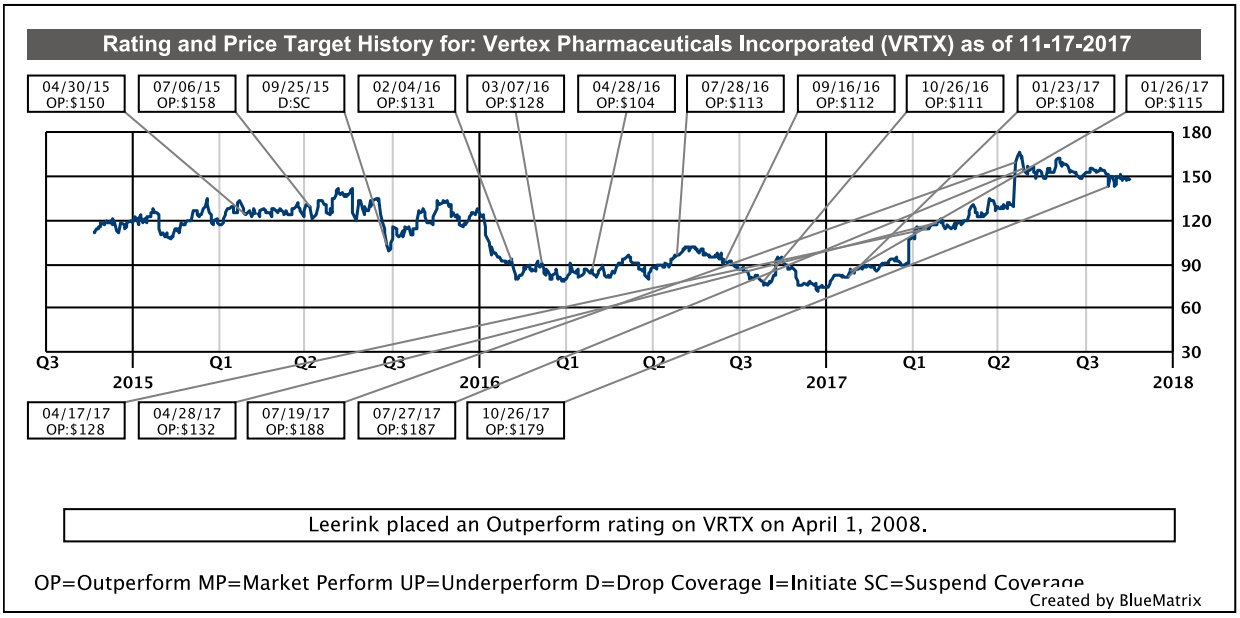

Leerink placed an Outperform rating on VRTX on April 1, 2008.

OP=Outperform MP=Market Perform UP=Underperform D=Drop Coverage I=Initiate SC=Suspend Coverage

Created by BlueMatrix

OP=Outperform MP=Market Perform UP=Underperform D=Drop Coverage I=Initiate SC=Suspend Coverage

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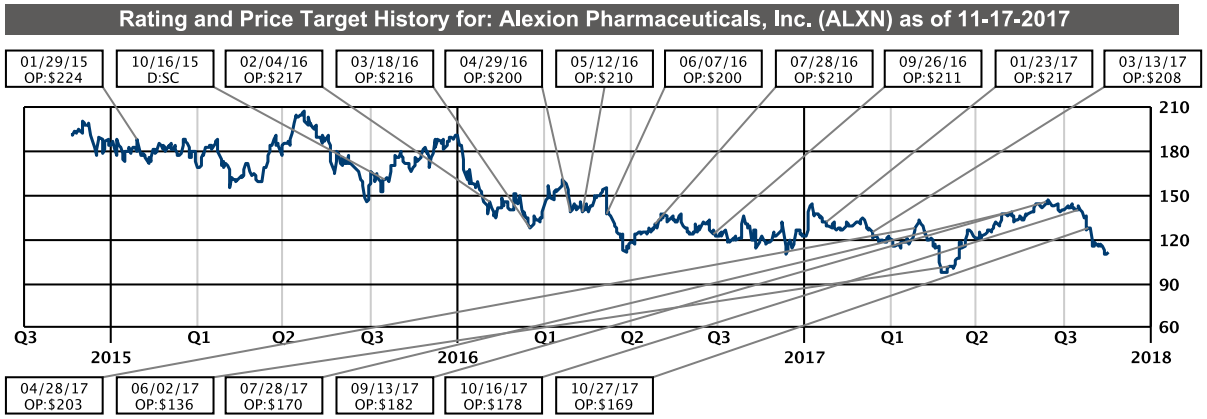
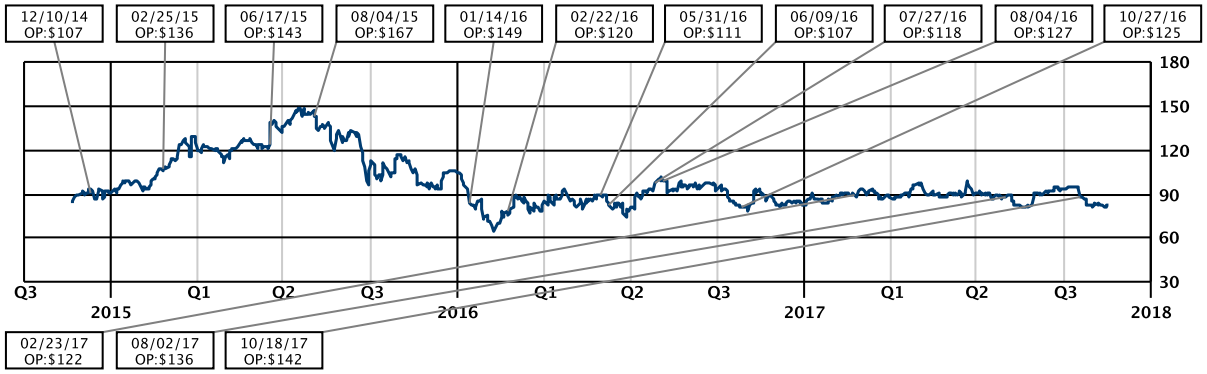


Leerink initiated coverage of ALXN with an Outperform rating on Feb. 9, 2009.

OP=Outperform MP=Market Perform UP=Underperform D=Drop Coverage I=Initiate SC=Suspend Coverage

Created by BlueMatrix



On June 27, 2005 Leerink placed an Outperform rating on BMRN.

OP=Outperform MP=Market Perform UP=Underperform D=Drop Coverage I=Initiate SC=Suspend Coverage

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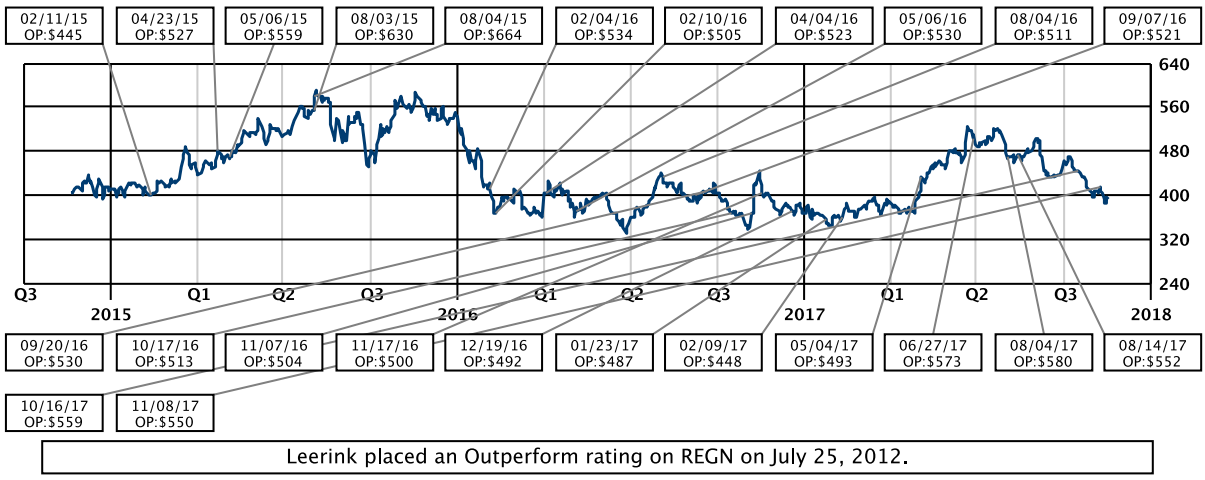
Rating and Price Target History for: Regeneron Pharmaceuticals, Inc. (REGN) as of 11-17-2017
02/11/15 OP:$445
04/23/15 OP:$527
05/06/15 OP:$559
08/03/15 OP:$630
08/04/15 OP:$664
02/04/16 OP:$534
02/10/16 OP:$505
04/04/16 OP:$523
05/06/16 OP:$530
08/04/16 OP:$511
09/07/16 OP:$521
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05/04/17 OP:$493
06/27/17 OP:$573
08/04/17 OP:$580
08/14/17 OP:$552
10/16/17 OP:$559
11/08/17 OP:$550
Leerink placed an Outperform rating on REGN on July 25, 2012.
OP=Outperform MP=Market Perform UP=Underperform D=Drop Coverage I=Initiate SC=Suspend Coverage
Created by BlueMatrix

Distribution of Ratings/Investment Banking Services (IB) as of 09/30/17				
			IB Serv./Past 12 Mos.	
Rating	Count	Percent	Count	Percent
BUY [OP]	122	67.4	40	32.8
HOLD [MP]	59	32.6	4	6.8
SELL [UP]	0	0.00	0	0

Explanation of Ratings

Outperform (Buy): We expect this stock to outperform its benchmark over the next 12 months.

Market Perform (Hold/Neutral): We expect this stock to perform in line with its benchmark over the next 12 months.

Underperform (Sell): We expect this stock to underperform its benchmark over the next 12 months.

The degree of outperformance or underperformance required to warrant an Outperform or an Underperform rating should be commensurate with the risk profile of the company.

For the purposes of these definitions the relevant benchmark will be the S&P 600® Health Care Index for issuers with a market capitalization of less than $2 billion and the S&P 500® Health Care Index for issuers with a market capitalization over $2 billion.

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Important Disclosures

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Leerink Partners LLC makes a market in Vertex Pharmaceuticals Incorporated, AbbVie Inc., Alexion Pharmaceuticals, Inc., BioMarin Pharmaceutical Inc. and Regeneron Pharmaceuticals, Inc.

Leerink initiated coverage of ALXN with an Outperform rating on Feb. 9, 2009.

On June 27, 2005 Leerink placed an Outperform rating on BMRN.

Leerink placed an Outperform rating on REGN on July 25, 2012.

Leerink placed an Outperform rating on VRTX on April 1, 2008.

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