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EQUITY RESEARCH
Company Report

May 11, 2018

Ionis Pharmaceuticals (IONS - $42.80)

Healthcare/Biotechnology

AdComm Voted in Favor of Waylivra Approval After Intense Discussions on the Benefits and Risks

Ticker:	**IONS**
Rating:	**Buy**
Price Target:	**$65.00**

Yesterday the FDA Endocrinology and Metabolic Drugs Advisory Committee voted 12 to 8 with no abstention in favor of Waylivra approval. The PDUFA date is scheduled on August 30, 2018.

- **Details** After a full day of deliberation, the FDA Endocrinology and Metabolic Drugs Advisory Committee voted 12 to 8 in favor of Waylivra (formerly volanesorsen**)** approval for treating familial chylomicronemia syndrome (FCS). The briefing document released on May 8 highlighted some of the agency's concerns, mainly focusing on the occurrence of severe thrombocytopenia with the possibility of serious bleeding. The document also asked about the sufficiency of the monitoring plan and the REMS program for managing this risk. The agency recognized the efficacy of Waylivra in lowering fasting triglyceride levels markedly and the unmet need in FCS, with Waylivra potentially as the first drug to treat this problem. Overall, just like all other drugs, it is a risk/benefit assessment for Waylivra in FCS. To that end, besides the favorable vote, FDA and Akcea agreed to establish a REMS program. AKCA management also indicated that the company will setup additional measures, like nursing case managers, in-home phlebotomy services and automated alerts to potentially further safeguard patients from AEs. Shares of IONS and AKCA were both halted yesterday due to the AdComm meeting.
- **Implications.** As we have mentioned before in our previous note that the safety, mainly thrombocytopenia, not the efficacy (77% vs. 18% in mean triglyceride reduction, $p<0.0001$ and decreased risk in pancreatitis) or unmet need would be the focus of discussion and disagreements. Such a scenario played out yesterday. We also believe the two opposing sides of the panel votes were mainly split between the group with a comfort on the risk management program and those who still have concern. Although the difference between the supported and the opposed votes were narrower than we have estimated; we continue to believe the FDA is likely to approve Waylivra at or before the PDUFA date, mainly because of the unmet need of such a rare disease and efficacy of the drug. AKCA indicated an immediate product launch if approved.
- **Action.** We are reiterating our Buy rating and $65 target price to reflect our bullish view on progress in IONS's marketed and pipeline products. Our valuation is based on our DCF and probability-adjusted-NPV-driven, sum-of-the-parts analyses.

Trading Data:

Last Price (5/9/2018)	$42.80
52–Week High (10/20/2017)	$65.51
52–Week Low (5/8/2018)	$39.07
Market Cap. (MM)	$5,372
Shares Out. (MM)	126.098

Earnings Estimates: (per share)

(Dec)	1Q	2Q	3Q	4Q	FY	P/E
FY-18E	-0.01A	-0.06	0.11	0.31	0.35	NM
FY-17A	0.03	-0.09	0.00	0.02	0.08	NM
FY-16A	-0.52	-0.47	0.06	0.21	-0.72	NM
FY-15A	-0.14	0.30	-0.30	-0.59	-0.74	NM

Source: Laidlaw & Company estimates

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Anticipated milestones in 2018 and beyond

Product	Indication	Event	Timing	Importance
IONIS-APOCIII$_{Rx}$ (Waylivra or volanesorsen)	Familiar chylomicronemia syndrome (FCS)	PDUFA date	**8/30/2018**	****
		Product launch	**2H18**	***
	Familiar partial lipodystrophy (FPL)	Completion of patient recuritment of Phase III study	**2018**	***
		Report of Phase III study top-line results	**2019**	****
Spinraza (Nusinersen)	Spinal muscular atrophy (infant /children)	Potential additional ROW approvals	**2018**	***
		Quarterely sales updates (recurring)	**2018**	***
IONIS-TTR$_{Rx}$ (Tegsedi or inotersen)	Polyneuropathy due to hereditary TTR amyloidosis (hATTR-PN)	PDUFA date	**10/6/2018**	****
		Potential launch	**4Q18**	****
IONIS-TTR-L$_{Rx}$	Cardiomyopathy due to TTR amyloidosis	Possibly start Phase I study	**2H18**	***
IONIS-FXI$_{Rx}$	Atrial fibrillation of end-stage renal disease	Potential to report Phase IIb ESRD dose optimizing study	**2019**	***
		Potential to start Phase III study or decision waiting for Lica product by Bayer	**2019**	***
IONIS-FXI-L$_{Rx}$	Novel anti-thrombotic agent	Potential to start Phase I study	**2018**	***
		Potential to report Phase I study results	**2019**	***
ACKEA-APOCIII-L$_{Rx}$	High risk CV patients with elevated triglyceride as major risk factor	Report Phase II dose optimization study results	**2019**	****
		NVS start Phase III CV outcome study	**2019**	****
IONIS-DMPK-2.5$_{Rx}$	Myotonic dystrophy 1	Develop the next gen. product	**2018**	***
IONIS-PKK$_{Rx}$	Hereditary angioedema	Possibly to start a LICA version drug Phase I trial	**2018**	***
IONIS-HTT$_{Rx}$	Huntington disease	Potentially start Phase II/III study by Roche	**2H18**	***
ACKEA-ANGPTL3-L$_{Rx}$	Rare hyperlipidermias	Potentially report Phase II study results	**2018**	***
	Non-alcoholic fatty liver disease (NAFLD) with metabolic complications	Potentially report Phase II study results	**2018**	***
IONIS-TMPRSS6-L$_{Rx}$	β-Thalassemia	Phase I study results	**2018**	***
ACKEA-APO(a)-L$_{Rx}$	High risk CV patients with elevated Lp(a) as major risk factor	Report Phase II dose optimization study results	**2H18**	****
		NVS start Phase III CV outcome study	**2019**	****
IONIS-STAT3-2.5$_{Rx}$ (Danvatirsen)	Head and neck cancer	Report Phase I/II study results	**2H18**	***
IONIS-DGAT2-L$_{Rx}$	NASH	Report Phase II study results	**2H18**	***
IONIS-SOD1$_{Rx}$	Amyotrophic lateral sclerosis	Report Phase I/II study results	**4Q18/2019**	***
IONIS-BIIB4 - 6$_{Rx}$	Neurodegenerative disease	Report Phase I study results	**2018**	***
IONIS-GHR-L$_{Rx}$	Acromegaly	Phase II study results	**2H18**	***
IONIS-AGT-L$_{Rx}$	Treatment-resistant hypertension	Phase Ib study results	**2H18**	***
IONIS-FB-L$_{Rx}$	Complement-mediated diseases	Start Phase II study	**2018**	***
IONIS-HBV$_{Rx}$	HBV	Potentially report Phase II study top-line results	**2018**	****
IONIS-AR-2.5$_{Rx}$	Cancer	Start Phase II study with AZN	**2018**	***
IONIS-KRAS-2.5$_{Rx}$	Cancer	Start Phase II study with AZN	**2018**	***

***** / ***** Major catalyst event that could impact share price very significantly while *** event is more informative*

Source: Laidlaw & Company estimates and company presentation.

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Major risks

Clinical risks of study failure could have significant impacts on IONS share value. Although many ongoing studies have provided encouraging clinical outcomes following prior studies; risks remain that some current trials might not meet study endpoints in order to advance forward. As such, the value of any such clinical asset could be significantly impaired and therefore IONS shareholder value could diminish. Such a negative impact could be more pronounced if the clinical program is in very advanced development stages or with high investor expectations. Regulatory risks are part of the clinical risks as even if a drug met its endpoints for pivotal studies. The regulatory agency might not grant approval and therefore, the drug cannot be commercialized.

Commercial risk even if a therapeutic is approved, sales could be substantially below expectations. Even it is approved; the commercial sales of any drug could fall below expectations, resulting in diminishing IONS shareholder value. Factors that could impact on the commercial outlook of a drug could include execution of marketing and sales; competition from other drugs; potential change of the treatment paradigm; and unrealistic expectations or projections.

Continued consummations of partnerships could be important. Given that partnerships are a critical part of IONS product development and commercialization strategy; failure to consummate future product development or product commercialization partnerships could put share value at risk. The alternative approach could require that the company raise capital from financial markets to support its operation if the company cannot generate profits from product revenues.

Future capital raises could potentially dilute value of current shareholders. If it is not profitable, the company may need to raise capital from financial markets to support its operations; even if the company already has partners to provide milestone and other types of payments and/or product revenue. As such, the company might not always be able to raise capital from financial markets at favorable terms. Share dilution under this scenario could reduce the value of the investment to current shareholders of the company

Although antisense drugs have been approved, this modality might not be broadly accepted and therefore limit its commercial potential. Although two antisense drugs are already approved and commercialized in the U.S. and other part of the world; this treatment modality remains with limited exposure to the medical world. As such, it is possible that going forward, antisense or other RNA-based medication could have limited use due to market acceptance. Such a scenario could reduce the market potential of antisense drugs and have negative impact on IONS shareholder value.

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Figure 1: Income Statement

Ionis Pharmaceuticals – Income Statement

($'MM)	2014	2015	2016	2017	1Q18	2Q18E	3Q18E	4Q18E	2018E	2019E	2020E
Revenue											
IONIS-TTR$_{Rx}$ (Inotersen, Tegsedi) revenue			0.0	0.0	-	-	-	16.3	16.3	233.5	348.8
IONIS-APOCIII$_{Rx}$ & L$_{Rx}$ (Volanesorsen or Waylivra) revenue			0.0	0.0			3.3	7.3	10.6	49.1	78.1
Spinraza (Nusinersen) revenue			0.0	112.5	41.1	45.4	52.6	53.4	192.5	256.4	290.6
Pipeline products - Prob. Adj					-	-	-	-	0.0	14.6	68.5
R&D revenue under collaborative agreements	202.5	281.4	325.9	385.6	102.4	96.0	109.0	114.0	421.4	401.8	385.7
Licensing and royalty revenue	11.6	2.3	20.7	9.5	0.9	1.0	1.5	1.8	5.2	5.2	5.2
Total revenue	214.2	283.7	346.6	507.7	144.4	142.4	166.3	192.9	646.0	960.6	1,177.1
Costs of goods							0.4	2.8	3.2	33.9	51.2
Research and development	241.8	322.3	344.3	374.6	104.1	98.9	94.9	96.8	394.6	410.4	426.9
General and administrative	20.1	37.2	48.6	108.5	43.7	49.3	55.2	60.2	208.4	227.2	245.4
Total Operating Expenses	261.9	359.5	392.9	483.1	147.7	148.2	150.5	159.9	606.3	671.5	723.5
Operating Incomes (losses)	(47.7)	(75.8)	(46.3)	24.5	(3.3)	(5.8)	15.8	33.0	39.7	289.0	453.6
Equity in net loss of Regulus Therapeutics Inc.											
Investment income	2.7	4.3	5.5	8.2	3.6	3.4	3.3	3.1	13.4	14.8	16.2
Interest expense	(22.2)	(36.7)	(38.8)	(44.8)	(10.9)	(11.0)	(11.7)	(11.3)	(44.9)	(49.4)	(49.4)
Gain on investments, net	1.8	0.1	(0.0)	0.0	0.0	0.0	0.0	0.0	0.0	(27.0)	(27.0)
Gain on investment in Regulus Therapeutics Inc.	19.4	20.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Loss on extinguishment of financing liability for leased facility				(7.7)							
Loss on early retirement of debt	(8.3)		(4.0)	0.0							
Other expenses				(3.5)	(0.2)	(2.0)	(2.0)	(2.0)	(6.2)	(6.5)	(6.8)
Total Other Income, net	(6.7)	(12.1)	(37.3)	(47.8)	(7.5)	(9.6)	(10.4)	(10.2)	(31.5)	(61.7)	(60.2)
Income before tax	(54.4)	(87.9)	(83.6)	(23.2)	(10.8)	(15.4)	5.4	22.8	2.0	227.4	393.4
Tax	15.4	(0.4)	(2.9)	6.0	(0.0)	0.0	2.0	8.4	10.4	(84.1)	(145.6)
Net Income (Loss) GAAP	(39.0)	(88.3)	(86.6)	(17.3)	(10.8)	(15.4)	7.4	31.2	12.4	143.2	247.8
Net loss attributable to noncontrolling interest in Akcea				11.3	9.4	8.4	7.0	7.2	32.0	33.6	35.3
Net Income (Loss) Applicable to Common Shareholders	(39.0)	(88.3)	(86.6)	(5.9)	(1.4)	(7.0)	14.4	38.4	44.4	176.8	283.1
Net Earnings (Losses) Per Share—Basic and Diluted	($0.33)	($0.74)	($0.72)	$0.08	($0.01)	($0.06)	$0.11	$0.31	$0.35	$1.39	$2.19
Shares outstanding—basic	117.7	119.7	120.9	124.0	125.3	125.4	125.6	125.8	125.5	127.5	129.5
Shares outstanding--diluted	118.8	119.7	120.9	126.1	125.3	125.4	125.6	125.8	125.5	127.5	129.5
Margin Analysis (% of Sales/Revenue)											
Costs of goods			0%	0%					0%	0%	0%
R&D	113%	114%	99%	74%	72%	69%	57%	50%	61%	43%	36%
MG&A	9%	13%	14%	21%	30%	35%	33%	31%	32%	24%	21%
Operating Income (loss)	-22%	-27%	-13%	5%	-2%	-4%	9%	17%	6%	30%	39%
Net Income	-18%	-31%	-25%	-1%	-1%	-5%	9%	20%	7%	18%	24%
Financial Indicator Growth Analysis (YoY%)											
R&D revenue under collaborative agreements	40%	39%	16%	18%	1%	18%	25%	-1%	9%	-2%	-4%
Licensing and royalty revenue	277%	-80%	784%	-54%	-73%	80%	71%	-60%	-45%	0%	0%
Total Revenue	45%	32%	22%	46%	31%	37%	38%	12%	27%	49%	23%
R&D	31%	33%	7%	9%	26%	18%	18%	-25%	5%	4%	4%
SG&A	35%	85%	31%	123%	219%	121%	106%	32%	92%	9%	8%
Marketing and sales									5%	6%	5%
Operating Loss	-8%	59%	-39%	-153%	-124%	246%	13%	-2050%	62%	628%	57%
Total Other Income, net	-55%	82%	207%	28%	421%	3%	-42%	1%	-34%	96%	-2%
Pretax Income	-18%	62%	-5%	-72%	-411%	40%	-237%	-293%	-109%	11236%	73%
Net Income	-36%	126%	-2%	-93%	-141%	-38%	-1573%	1301%	-848%	298%	60%
EPS	-40%	123%	-3%	-111%	-141%	-38%	5219%	1291%	342%	292%	58%

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Source: Bloomberg LP; Company reports; Laidlaw & Company estimates.

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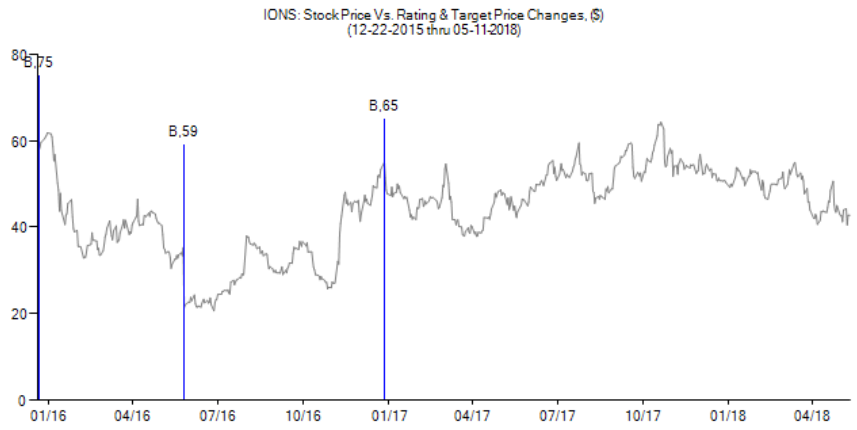
Rating and Price Target Change History



3 Year Rating Change History

Date	Rating	Closing Price ($)
12/22/...	Buy (B)	57.85

3 Year Price Change History

Date	Target Price ($)	Closing Price, ($)
12/22/...	75.00	57.85
05/26/...	59.00	21.36
12/27/...	65.00	55.12

Source: Laidlaw & Company Created by: Blue-Compass.net
Note: Company changed its ticker symbol to IONS from ISIS on 12/22/2015.

Laidlaw & Company Rating System*		% of Companies Under Coverage With This Rating	% of Companies for which Laidlaw & Company has performed services for in the last 12 months	
			Investment Banking	Brokerage
Strong Buy (SB)	Expected to significantly outperform the sector over 12 months.	0.00%	0.00%	0.00%
Buy (B)	Expected to outperform the sector average over 12 months.	66.67%	25.93%	3.70%
Hold (H)	Expected returns to be in line with the sector average over 12 months.	0.00%	0.00%	0.00%
Sell (S)	Returns expected to significantly underperform the sector average over 12 months.	0.00%	0.00%	0.00%

ADDITIONAL COMPANIES MENTIONED

Akcea (AKCA – Not Rated)

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