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EQUITY RESEARCH
Company Report

April 2, 2018

Ionis Pharmaceuticals (IONS - $44.08)

Healthcare/Biotechnology

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

Potential Entry of Tafamidis in the U.S. Making the TTR Market Dynamics Much More Interesting

Pfizer reported last Thursday that the tafamidis in transthyretin cardiomyopathy (TTR-CM) Phase III (ATTR-ACT) study met its primary endpoint of a statistically significant reduction in all-cause mortality and frequency of cardiovascular-related hospitalizations vs. placebo at 30 months.

- **Details.** The details of the Phase III data are not available and Pfizer expects to present them at an upcoming medical conference. The ATTR-ACT study is a double-blind, placebo-controlled, randomized and 441-patient clinical trial evaluating oral daily dose of 20 mg or 80 mg tafamidis capsules compared to placebo. The study included both the hereditary and wild-type (non-hereditary) form of patients. Tafamidis is approved in Europe (brand name: Vyndaqel) for TTR familial amyloid polyneuropathy but not in the U.S. PFE plans to discuss with health authorities to determine an appropriate regulatory path forward.
- **Implications.** Given that achieving a MACE type of endpoint is the gold standard for cardiovascular medication development, the ATTR-ACT study outcomes bode well for the potential additional approval in EU and possibly approval in the U.S. (possibly in TTR-CM only). We estimate a possible timeline for the U.S. approval could be in early 2019. Given the solid Phase III study readout of inotersen as well as Patisiran from ALNY, we believe both drugs should still have a very strong penetration of the amyloid polyneuropathy (TTR-AP) market, especially given the poor performance of Vyndaqel in EU so far. Near term, tafamidis could potentially be competitive in patients with mixed polyneuropathy and cardiomyopathy symptoms and might have a greater competitive edge in patients with wild-type cardiomyopathy. Longer term, IONS is advancing its LICA drug (AKCEA-TTR-L_{Rx}) into clinical study in TTR-CM in 2H18. Although tafamidis and inotersen (or its next gen product) have different mechanisms, we believe the positive MACE benefits tafamidis has demonstrated could also potentially be seen in an antisense drug. This notion could be supported by the encouraging follow-up from Dr. Merrill Benson's small (n=30) open-label inotersen in TTR-CM study. Also, indirectly, tafamidis showed more modest TTR-AP clinical effect (NIS-LL of 45% vs. 30%, p=0.068) vs. inotersen (mNIS+7 with p=0.0005 at month 8). IONS might develop AKCEA-TTR-L_{Rx} in hereditary TTR-CM the same way as in TTR-AP, and in wild-type based on MACE-type endpoints.
- **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 (3/29/2018)	$44.08
52–Week High (10/20/2017)	$65.51
52–Week Low (4/6/2017)	$37.26
Market Cap. (MM)	$5,343
Shares Out. (MM)	126.09

Earnings Estimates: (per share)

(Dec)	1Q	2Q	3Q	4Q	FY	P/E
FY-18E	-0.23	-0.20	-0.15	0.07	-0.52	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

Yale Jen, Ph.D.
Managing Director /
Senior Biotechnology Analyst
(212) 953-4978
yjen@laidlawltd.com

Anticipated milestones in 2018 and beyond

Product	Indication	Event	Timing	Importance
IONIS-APOCIII$_{Rx}$ (Volanesorsen)	Familiar chylomicronemia syndrome (FCS)	AdComm meeting	**5/10/2018**	****
		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$_{Rx}$ (Inotersen)	Polyneuropathy due to hereditary TTR amyloidosis (hATTR-PN)	PDUFA date	**7/6/2018**	****
		Potential ex-U.S. partnership	**2018**	***
		Potential approval	**Mid-18**	****
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	**2018/2019**	***
		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**	***
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	**2017**	***
IONIS-PKK$_{Rx}$	Hereditary angioedema	Possibly to start a LICA version drug Phase I trial	**2018**	***
IONIS-HTT$_{Rx}$	Huntington disease	Report Phase I/IIa study results at the AAN meeting	**4/21-27/2018**	***
		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-DGAT2$_{Rx}$	NASH	Report Phase II study results	**2018**	***
IONIS-SOD1$_{Rx}$	Amyotrophic lateral sclerosis	Report Phase I/II study results	**2018**	***
IONIS-BIIB4 - 6$_{Rx}$	Neurodegenerative disease	Report Phase I study results	**2018**	***
IONIS-GHR-L$_{Rx}$	Acromegaly	Phase II study results	**2018**	***
IONIS-AGT-L$_{Rx}$	Treatment-resistant hypertension	Phase Ib study results	**2018**	***
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.

Yale Jen, Ph.D.
yjen@laidlawltd.com

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.

Yale Jen, Ph.D.
yjen@laidlawltd.com

Figure 1: Income Statement

Ionis Pharmaceuticals – Income Statement

($'MM)	2014	2015	2016	2017	1Q18E	2Q18E	3Q18E	4Q18E	2018E	2019E	2020E
Revenue											
IONIS-TTR$_{Rx}$ (Inotersen) revenue			0.0	0.0	-	-	16.3	32.6	48.9	233.5	348.8
IONIS-APOCIII$_{Rx}$ & L$_{Rx}$ (Volanesorsen) revenue			0.0	0.0			3.3	7.3	10.6	49.1	78.1
Spinraza (Nusinersen) revenue			0.0	112.5	38.4	45.4	52.6	53.4	189.8	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	85.0	91.0	84.0	99.0	359.0	351.8	337.7
Licensing and royalty revenue	11.6	2.3	20.7	9.5	2.0	1.0	1.5	1.8	6.3	6.3	6.3
Total revenue	214.2	283.7	346.6	507.7	125.4	137.4	157.6	194.2	614.6	911.6	1,130.1
Costs of goods							2.3	4.8	7.1	33.9	51.2
Research and development	241.8	322.3	344.3	374.6	101.3	102.4	106.5	108.6	418.7	435.5	452.9
General and administrative	20.1	37.2	48.6	108.5	47.1	54.1	60.6	66.1	227.9	248.5	268.3
Total Operating Expenses	261.9	359.5	392.9	483.1	148.4	156.5	169.4	179.5	653.8	717.9	772.5
Operating Incomes (losses)	(47.7)	(75.8)	(46.3)	24.5	(23.0)	(19.1)	(11.8)	14.7	(39.2)	193.8	357.6
Equity in net loss of Regulus Therapeutics Inc.											
Investment income	2.7	4.3	5.5	8.2	2.5	2.5	2.5	2.5	10.0	11.0	12.1
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)	(2.0)	(2.0)	(2.0)	(2.0)	(8.0)	(8.4)	(8.8)
Total Other Income, net	(6.7)	(12.1)	(37.3)	(47.8)	(10.4)	(10.5)	(11.2)	(10.8)	(34.9)	(65.4)	(64.3)
Income before tax	(54.4)	(87.9)	(83.6)	(23.2)	(33.4)	(29.6)	(23.0)	3.9	(82.1)	128.4	293.3
Tax	15.4	(0.4)	(2.9)	6.0	0.0	0.0	0.0	1.4	1.4	(47.5)	(108.5)
Net Income (Loss) GAAP	(39.0)	(88.3)	(86.6)	(17.3)	(33.4)	(29.6)	(23.0)	5.3	(80.7)	80.9	184.8
Net loss attributable to noncontrolling interest in Akcea				11.3	4.0	4.0	4.0	4.0	16.0	16.8	17.6
Net Income (Loss) Applicable to Common Shareholders	(39.0)	(88.3)	(86.6)	(5.9)	(29.4)	(25.6)	(19.0)	9.3	(64.7)	97.7	202.4
Net Earnings (Losses) Per Share—Basic and Diluted	($0.33)	($0.74)	($0.72)	$0.08	($0.23)	($0.20)	($0.15)	$0.07	($0.52)	$0.77	$1.57
Shares outstanding—basic	117.7	119.7	120.9	124.0	124.8	124.9	125.1	125.3	125.0	127.0	129.0
Shares outstanding--diluted	118.8	119.7	120.9	126.1	126.9	126.9	127.1	127.3	127.0	129.0	131.0
Margin Analysis (% of Sales/Revenue)											
Costs of goods			0%	0%					0%	0%	0%
R&D	113%	114%	99%	74%	81%	74%	68%	56%	68%	48%	40%
MG&A	9%	13%	14%	21%	38%	39%	38%	34%	37%	27%	24%
Operating Income (loss)	-22%	-27%	-13%	5%	-18%	-14%	-7%	8%	-6%	21%	32%
Net Income	-18%	-31%	-25%	-1%	-23%	-19%	-12%	5%	-11%	11%	18%
Financial Indicator Growth Analysis (YoY%)											
R&D revenue under collaborative agreements	40%	39%	16%	18%	-16%	12%	-4%	-14%	-7%	-2%	-4%
Licensing and royalty revenue	277%	-80%	784%	-54%	-44%	80%	71%	-60%	-34%	0%	0%
Total Revenue	45%	32%	22%	46%	14%	32%	30%	13%	21%	48%	24%
R&D	31%	33%	7%	9%	23%	23%	33%	-15%	12%	4%	4%
SG&A	35%	85%	31%	123%	244%	143%	126%	45%	110%	9%	8%
Marketing and sales									5%	6%	5%
Operating Loss	-8%	59%	-39%	-153%	-265%	1043%	-185%	-968%	-260%	-594%	85%
Total Other Income, net	-55%	82%	207%	28%	623%	13%	-37%	7%	-27%	87%	-2%
Pretax Income	-18%	62%	-5%	-72%	-1064%	169%	485%	-133%	253%	-256%	128%
Net Income	-36%	126%	-2%	-93%	-948%	128%	1848%	240%	989%	-251%	107%
EPS	-40%	123%	-3%	-111%	-935%	123%	-7050%	234%	-747%	-249%	104%

Yale Jen, Ph.D. 212-953-4978

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

Yale Jen, Ph.D.
yjen@laidlawltd.com

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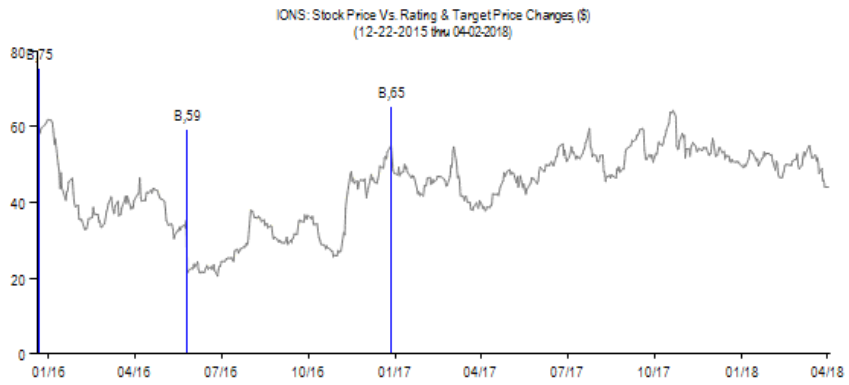
Rating and Price Target Change History



3 Year Rating Change History

Date	Rating	Closing Price ($)
12/22/2015	Buy (B)	57.85

3 Year Price Change History

Date	Target Price ($)	Closing Price, ($)
12/22/2015	75.00	57.85
05/26/2016	59.00	21.36
12/27/2016	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.	64.71%	27.45%	3.92%
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

Pfizer (PFE – Not Rated)
Alnylam Pharmaceuticals (ALNY – Not Rated)
Akcea Therapeutics (AKCA – Not Rated)

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Yale Jen, Ph.D.
yjen@laidlawltd.com

NOTES:

Yale Jen, Ph.D.
yjen@laidlawltd.com