

Ionis Pharmaceuticals (IONS - \$41.27)

Healthcare/Biotechnology

1Q18: Waylivra AdComm Meeting This Week and We Expect Recommendation for Approval

IONS reported 1Q18 financial results last Friday with net loss of (\$1.4MM) vs. our (\$29.4MM) and the Street's (\$23.4MM). Loss/share was (\$0.01) vs. (\$0.23) and (\$0.16) for Laidlaw and the Street, respectively. IONS currently has \$2 billion cash: \$1 billion by end of 1Q18 combined with \$1 billion from the recent BIIB deal.

- Waylivra (former volanesorsen) AdComm meeting the most near-term event.** IONS formally named volanesorsen Waylivra. The FDA Endocrinology and Metabolic Drugs Advisory Committee will hold a panel on Waylivra on May 10, with a briefing document expected available on May 8. We do not expect the efficacy of Waylivra to be questioned much given the robust results from the APPROACH study in FCS (77% vs. 18% in mean triglyceride reduction, $p < 0.0001$). We also anticipate the panel will recommend for approval and the FDA will likely come to the same decision given the risk/reward profile of the drug and the unmet need. We believe a good portion of the discussion might be centered around safety, such as severe thrombocytopenia, monitoring and potential dosing adjustment. Given all the available clinical results, we believe the sentiment of investors is that approval of Waylivra is highly likely.
- Tegsedi (formerly inotersen) PDUFA date push out to 10/06/2018 from 7/6/2018.** Both Akcea and IONS earnings press releases have reported that the Tegsedi PDUFA date has been pushed out to 10/06/2018 from 07/06/2018. Although this decision has possibly moved the potential approval of Tegsedi to after that of Patisiran; the overall impact on Tegsedi might not be much, if any. Given the intervening period between the two potential product launches is relatively short (possibly less than 2 months), the most critical factors likely determining the market share dynamics would be the various attributes of each drug.
- 2018 P&L guidance.** IONS indicated that the 2018 pro forma guidance for the R&D expenses is \$360 – \$390MM and SG&A expenses is \$180 – \$210MM.
- Neurological pipeline development update.** Coupled with the recent deal with BIIB in neurological diseases, IONS will also develop their in-house neurological programs that the company could potentially commercialize on its own. Several indications mentioned include Lafora disease, Alexander disease and Charcot-Marie-Tooth. Some of those programs could start in 2019.
- 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.

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

Trading Data:

Last Price (5/4/2018)	\$41.27
52-Week High (10/20/2017)	\$65.51
52-Week Low (4/6/2018)	\$40.33
Market Cap. (MM)	\$5,521
Shares Out. (MM)	126.10

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

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Source: Laidlaw & Company estimates

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- Pipeline of other disease areas developments update.** In addition to IONIS-HTT_{Rx} (RG6042) in Huntington's disease pivotal study by Roche which could start later this year; AstraZeneca also has several collaborations starting to advance into later clinical development stages. IONIS-STAT3-2.5_{Rx} (Danvatirsen) in combination with Imfinzi (PD-L1 inhibitor) in head and neck cancer Phase I/II study is underway. Some study result updates could be available in 2018, possibly at the ESMO (10/19-23) or EORTC-NCI (11/13-16) meetings. In addition, IONIS-KRAS-2.5_{Rx} in cancer Phase II study is also ongoing.

Table 1: Estimated and reported 1Q18 results

1Q18 Estimates and Reported Results			
(\$ MM)	Laidlaw Estimate	Actual	Consensus
Total revenue	\$125.4	\$144.4	\$127.9
Total op. profit (loss)	(\$23.0)	(\$3.3)	(\$22.6)
R&D	\$101.3	\$104.1	
SG&A	\$47.1	\$43.7	
EPS	(\$0.23)	(\$0.01)	(\$0.16)
Net income (loss)	(\$29.4)	(\$1.4)	(\$23.4)

Source: Bloomberg, SEC filings and Laidlaw and Co.

Figure 1: Spinraza commercialization development in 1Q17-1Q18

U.S. Patient Dynamics*	Q1:17	Q2:17	Q3:17	Q4:17	Q1:18
Total patients	210	710	1,230	1,640	1,910
New patient starts	210	500	530	420	280
Average doses per patient	2.3	2.6	1.9	1.6	1.1
% Loading doses	100%	100%	90%	75%	60%
% Maintenance doses	0%	0%	10%	25%	40%
% Free doses	25%	20%	20%	20%	20%

Source: The company presentation

Anticipated milestones in 2018 and beyond

Product	Indication	Event	Timing	Importance
IONIS-APOCIII _{Rx} (Waylivra or 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 recruitment 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	***
		Quarterly 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 hyperlipidemias	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}	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.

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 if 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.

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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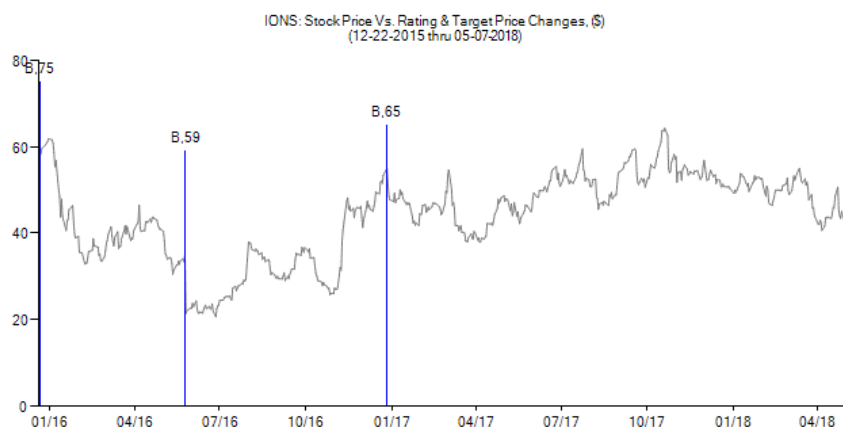
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3 Year Rating Change History

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.

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			Investment Banking	Brokerage
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ADDITIONAL COMPANIES MENTIONED

Akcea (AKCA – Not Rated)
Biogen (BIIB – Not Rated)
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