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EQUITY RESEARCH
Company Report

June 22, 2015

Isis Pharmaceuticals (ISIS - $ 62.55)

Healthcare/Biotechnology

Ticker:	**ISIS**
Rating:	**Buy**
Price Target:	**$ 75.00**

Second Robust Phase II Result Updates Further Strengthen Positive Outlook of ISIS-SMN$_{Rx}$ in SMA Development

This morning, ISIS updated investors with continued robust results of its ISIS-SMN$_{Rx}$ in childhood Phase II open label extension (OLE) study. The last prior update of the same patient cohort was September 2nd 2014.

- **Details.** The data cut-off for results reported today was May 15, 2015. Today's data updates are mainly of the OLE portion of the study where all patients were dosed at 12mg after they had been dosed at various doses (3, 6, 9 and 12mg) during earlier open label trial. The mean increase of Hammersmith Functional Motor Scale-Expanded (HFMSE) scores from baseline at ~9 months (260 days) were 3.8 points (n=22 all from prior 3, 6 and 9mg treatments). The increase was 4.4 (n=17) for patients with similar inclusion criteria (between 10 and 54) as the ongoing Phase III (CHERISH) study. In all, 57% of treated children achieved HFSME scores increases $\geq$ 3 points. Natural history data suggested patients on average experienced a one point HFMSE score decline per year. The six minute walk test (6MWT) of ambulatory patients increased 55 meters at ~9 months (n=11 all from prior 3, 6 and 9mg treatment). The mean change of upper limb module (ULM) test was maintained at a similar level of 2 points after the end of the open label study. On the safety side, ISIS-SMN$_{Rx}$ treatment is well tolerated and without drug-related serious adverse events.
- **Implication.** Following the recent ISIS-SMN$_{Rx}$ in infant Phase II study results update (06-11-2015); the childhood OLE results also exhibited a positive outcome as the drug demonstrated improving therapeutic benefits. It is encouraging, in our opinion, that regardless of the lower doses used during earlier open label study, all patients treated with 12mg (the same dose to be used for the Phase III trial) during the extension study have demonstrated substantial HFMSE score improvements. As such, we believe today's results further strengthen the likelihood of success of the ongoing Phase III study (primary endpoint is change in HFMSE score) consistent with the earlier positive childhood data report. CHERISH trial results are expected in late '16 or early '17.
- **Action.** We are reiterating our Buy rating and $75 price to reflect our bullish view on progress in ISIS's pipeline, especially ISIS-APOCIII$_{Rx}$, ISIS-SMN$_{Rx}$ and ISIS-TTR$_{Rx}$. Our valuation is based on our DCF and probability-adjusted-NPV-driven, sum-of-the-parts analyses.

Trading Data:

Last Price (06/19/2015)	$ 62.55
52–Week High (3/20/2015)	$ 77.80
52–Week Low (7/18/2014)	$ 27.37
Market Cap. (MM)	$ 7,488
Shares Out. (MM)	120

Earnings Estimates: (per share)

(Dec)	1Q	2Q	3Q	4Q	FY	P/E
FY-15E	-0.14A	0.48	-0.35	-0.31	-0.32	NM
FY-14A	-0.27	-0.10	-0.23	0.26	-0.33	NM
FY-13A	-0.02	-0.21	-0.21	-0.18	-0.55	NM
FY-12A	-0.24	-0.01	-0.37	0.01	-0.65	NM

Source: Laidlaw & Company estimates

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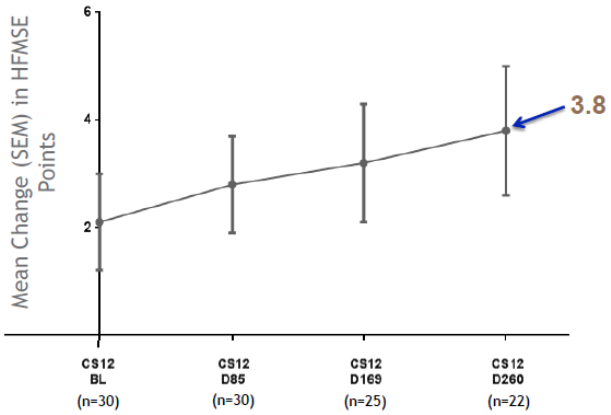
ISIS-SMN$_{Rx}$ in children Phase II study result updates

The data cut-off day for ISIS-SMN$_{Rx}$ in childhood Phase II study interim results was as of May 15, 2015. Figure 1 illustrates results of mean change of 3.8 points from baseline in HFMSE scores in ~ 9 months while all patients were dosed at 12 mg (n=22) at open label extension study. All 22 patients have been treated at 3, 6 or 9 mg during prior open label study. The results of the 12 mg treated patients were not mature enough to be counted for the 9 month analysis. The HFMSE score increase was 4.4 (n=17) for patients of similar inclusion criteria (between 10 and 54) as the ongoing Phase III or CHERISH study. As a reference, natural history study data suggested patients on average experienced one point HFMSE score decline per year if not treated.

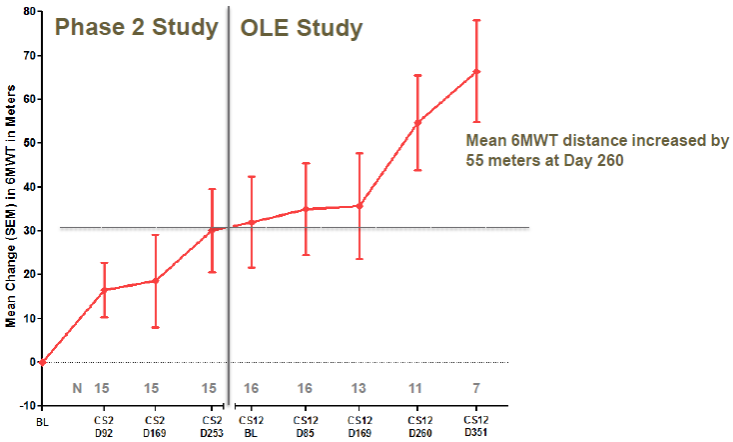
Figure 1: Mean change from baseline in HFMSE scores in ~ 9 months (260 D)



Source: Company presentation

The mean increase of the six minute walk test (6MWT) score of ambulatory patients was 55 meters in (n=11) (Figure 2).

Figure 2: Mean change from baseline in 6MWT for all ambulant subjects



Source: Company presentation

Figure 3 illustrates the mean changes in the upper limb module (ULM) test. The results demonstrated an increase of 2 points, which were achieved by the end of open label trial (n=10) and maintained nine months during the extension study (n=7). Overall, the ULM test is a relatively less sensitive assay where changes

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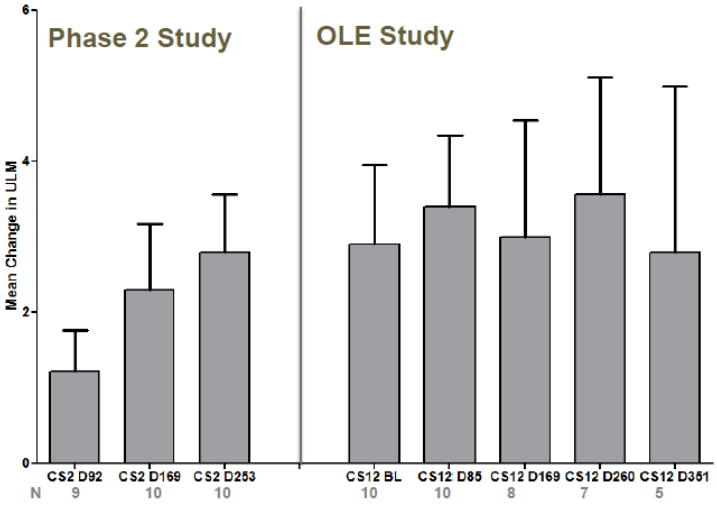
might not be properly measured under the scenario of a small sample size and with relatively modest differences.

Figure 3: Mean changes in upper limb module (ULM) test



Source: Company presentation

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Anticipated milestones in 2015 and beyond

Product	Indication	Event	Timing	Importance
Kynamro	Severe hetrogerous FH	Report of FOCUS FH Phase III study top-line results	**Mid-15**	***
ISIS-APOCIII$_{Rx}$	Familiar chylomicronemia syndrome (FCS)	Report of Phase III study top-line results	**1H17**	****
	Familiar partial lipodystrophy	Commencement of Phase III study	**Mid-15**	***
		Report of Phase III study top-line results	**2017**	****
	Spinal muscular atrophy (infant)	Report of Phase III study top-line results	**2H16/1H17**	****
	Spinal muscular atrophy (children)	Report of Phase III study top-line results	**2H16/1H17**	****
ISIS-TTR$_{Rx}$	Familiar amyloidosis polyneuropathy (FAP)	Completion of patient recuritment of Phase II/III study	**2H15/1H16**	***
		Commence Phase III study in Japan	**2H15**	***
		Report of Phase II/III study top-line results	**1H17**	****
		Report of interim analysis of ALN-TTR$_{IV}$ Apollo Phase III study by ALNY	**2017/2018**	***
		Potential approval	**Late 2017**	****
	Familiar amyloidosis cardiomyopathy (FAC)	Potential to start Phase II/III study	**2H15**	***
ISIS-FXI$_{Rx}$	Clotting disorders	Start Phase II study in atrial fibrillation of end-stage kidney disease patients	**Mid-15**	***
ISIS-APOCIII-L$_{Rx}$	Severely high triglyceride	Start Phase I study	**1Q16**	***
ISIS-DMPK$_{Rx}$	Myotonic dystrophy 1	Report Phase II proof-of-concept study data	**Late '15/2016**	****
ISIS-PKK$_{Rx}$	Hereditary angioedema	Start Phase II study	**Mid-15**	***
		Potentially report Phase II study top-line results	**2016**	****
ISIS-FGFR4$_{Rx}$	Obesity	Start II study	**2H15**	**
ISIS-DGAT2$_{Rx}$	NASH	Start I study	**2H15**	**
ISIS-HTT$_{Rx}$	Huntington disease	Start Phase I/II study	**Mid-15**	**
ISIS-GCGR$_{Rx}$	Diabetes	Start dose optimizing study	**2H15**	**
ISIS-PTP1B$_{Rx}$		Report detailed Phase II study results	**2H15**	***
ISIS-GCCR$_{Rx}$		Report Phase II study results	**2Q15**	***
	Cushing's syndrome	Potentially to start Phase II study	**2H15**	***
ISIS-ANGPTL3$_{Rx}$	Severe hyperlipidemia	Start Phase II study	**2H15**	***
ISIS-APO(a)$_{Rx}$	Severe high Lipoprotein(a)	Report Phase II study results	**2H15**	***
ISIS-APO(a)-L$_{Rx}$	Severe high Lipoprotein(a)	Start Phase I study	**1H15**	**
ISIS-BIIB3$_{Rx}$	Neurodegenerative disease	Start Phase I study	**2H15/16**	**
ISIS-GSK4$_{Rx}$	Ocular disease	Start Phase I study	**2H15**	**
ISIS-HBV$_{Rx}$	HBV	Complete Phase I study and potentially report results	**1H15**	***
		Initiate Phase II study	**Mid-15**	**
ISIS-STAT3$_{Rx}$	DLBCL	Report Phase II study results	**2H15**	***
		Potentially to start PD1 (MEDI4736) combination Phase II study	**2H15**	***
RG-101	HCV	Start mono and combo Phase II study	**2H15**	***
		Report Phase II study results	**2016**	***
		Report combo Phase II study results	**2016**	***
ISIS-AR$_{Rx}$	Prostate cancer	Report Phase I/II study results	**2H15**	***
EXC 001	Skin scarring	Potentially to report Phase IIb study data by PFE	**2016**	**
		Potential approval	**2020**	***
		Akcea business development update	**June 2015**	***

***** / ***** 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 ISIS 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 ISIS 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 ISIS 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 ISIS 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 ISIS shareholder value.

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Figure 1: Income Statement

Isis Pharmaceuticals – Income Statement

($'MM)	2012	2013	2014	1Q15	2Q15E	3Q15E	4Q15E	2015E	2016E	2017E	2018E	2019E	2020E
Revenue													
Kynamro profit share								0.0	3.7	16.8	26.0	34.7	40.3
ISIS-TTR$_{Rx}$ revenue									0.0	29.3	72.3	174.4	259.9
ISIS-APOCIII$_{Rx}$ revenue									0.0	3.6	66.2	157.5	225.9
ISIS-SMN$_{Rx}$ revenue									0.0	10.6	68.6	132.1	212.0
Pipeline products - Prob. Adj											5.8	31.4	81.5
R&D revenue under collaborative agreements	96.4	144.2	202.5	61.9	144.2	47.3	52.2	305.6	250.6	260.6	265.8	260.5	250.1
Licensing and royalty revenue	5.6	3.1	11.6	0.7	0.7	1.1	1.0	3.5	3.2	3.3	3.3	3.3	3.3
Total revenue	102.0	147.3	214.2	62.6	144.9	48.4	53.2	309.1	257.5	324.2	507.9	793.8	1,072.9
Research and development	158.5	184.0	241.8	64.4	70.9	73.0	73.7	282.1	304.7	326.0	342.3	356.0	370.2
General and administrative	12.5	14.9	20.1	7.5	7.6	7.8	8.0	30.8	31.8	34.6	37.8	41.1	44.4
Total Operating Expenses	171.0	199.0	261.9	71.9	78.5	80.8	81.7	313.0	336.4	360.6	380.1	397.1	414.7
Operating Incomes (losses)	(68.9)	(51.7)	(47.7)	(9.3)	66.4	(32.4)	(28.5)	(3.9)	(79.0)	(36.4)	127.9	396.6	658.3
Equity in net loss of Regulus Therapeutics Inc.	(1.4)	0.0											
Investment income	1.8	2.1	2.7	0.8	0.8	0.8	0.8	3.4	3.7	4.1	4.5	4.9	5.4
Interest expense	(21.2)	(19.4)	(22.2)	(9.0)	(9.0)	(9.0)	(9.0)	(36.1)	(37.2)	(40.9)	(45.0)	(49.5)	(49.5)
Gain on investments, net	1.5	2.4	1.8	-	0.0	-	-	0.0	1.9	(20.0)	24.0	(27.0)	(27.0)
Gain on investment in Regulus Therapeutics Inc.	18.4	0.0	19.4										
Loss on early retirement of debt	(4.8)	0.0	(8.3)										
Total Other Income, net	(5.7)	(14.9)	(6.7)	(8.2)	(8.2)	(8.2)	(8.2)	(32.7)	(31.5)	(56.8)	(16.5)	(71.5)	(71.0)
Income before tax	(74.6)	(66.6)	(54.4)	(17.5)	58.2	(40.6)	(36.7)	(36.6)	(110.5)	(93.2)	111.4	325.1	587.2
Tax	9.1	5.9	15.4	0.8	(1.0)	(1.0)	(1.0)	(2.2)	5.7	0.0	(41.2)	(120.3)	(217.3)
Net Income (Loss) GAAP	(65.5)	(60.6)	(39.0)	(16.7)	57.2	(41.6)	(37.7)	(38.8)	(104.8)	(93.2)	70.2	204.8	370.0
Net Income (Loss) Applicable to Common Shareholders	(65.5)	(60.6)	(39.0)	(16.7)	57.2	(41.6)	(37.7)	(38.8)	(104.8)	(93.2)	70.2	204.8	370.0
Net Earnings (Losses) Per Share—Basic and Diluted	($0.65)	($0.55)	($0.33)	($0.14)	$0.48	($0.35)	($0.31)	($0.32)	($0.86)	($0.75)	$0.56	$1.61	$2.86
Shares outstanding—basic and diluted	100.6	110.5	117.7	118.9	119.3	119.7	120.1	119.5	121.5	123.5	125.5	127.5	129.5
	100.6	110.5	118.8	118.9	119.3	119.7	120.1	119.5	121.5	123.5	125.5	127.5	129.5
Margin Analysis (% of Sales/Revenue)													
Costs of goods									0%	0%	0%	0%	0%
R&D	155%	125%	113%	103%	49%	151%	139%	91%	118%	101%	67%	45%	35%
MG&A	12%	10%	9%	12%	5%	16%	15%	10%	12%	11%	7%	5%	4%
Operating Income (loss)	-68%	-35%	-22%	-15%	46%	-67%	-54%	-1%	-31%	-11%	25%	50%	61%
Net Income	-64%	-41%	-18%	-27%	39%	-86%	-71%	-13%	-41%	-29%	14%	26%	34%
Financial Indicator Growth Analysis (YoY%)													
R&D revenue under collaborative agreements	0%	50%	40%	217%	155%	8%	-37%	51%	-18%	4%	2%	-2%	-4%
Licensing and royalty revenue	95%	-45%	277%	-92%	56%	315%	-57%	-70%	-8%	2%	1%	0%	0%
Total Revenue	3%	44%	45%	122%	154%	10%	-37%	44%	-17%	26%	57%	56%	35%
R&D	1%	16%	31%	21%	20%	20%	9%	17%	8%	7%	5%	4%	4%
SG&A	-2%	19%	35%	70%	71%	74%	17%	53%	3%	9%	9%	9%	8%
Operating Loss	-3%	-25%	-8%	-69%	-1098%	51%	-383%	-92%	1940%	-54%	-451%	210%	66%
Total Other Income, net	-59%	163%	-55%	110%	80%	116%	-247%	391%	-4%	80%	-71%	334%	-1%
Net Income	-23%	-7%	-36%	-47%	-574%	56%	-221%	-1%	170%	-11%	-175%	192%	81%
EPS	-23%	-16%	-40%	-47%	-567%	53%	-220%	-2%	166%	-13%	-174%	187%	78%

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

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Additional information available upon request.

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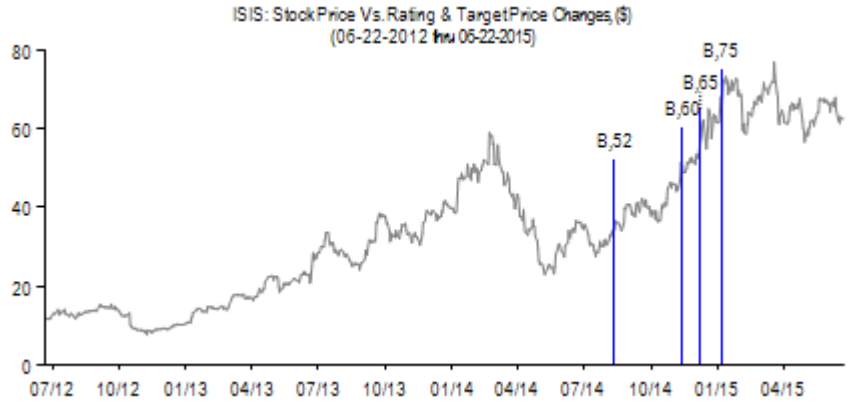
Rating and Price Target Change History



3 Year Rating Change History

Date	Rating	Closing Price ($)
08/12/2014	Buy (B)	34.40

3 Year Price Change History

Date	Target Price ($)	Closing Price, ($)
08/12/2014	52.00	34.40
11/13/2014	60.00	50.71
12/08/2014	65.00	56.99
01/06/2015	75.00	65.44

Source: Laidlaw & Company **Created by: Blue-Compass.net**

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.	75.00%	32.14%	7.14%
Hold (H)	Expected returns to be in line with the sector average over 12 months.	3.57%	0.00%	0.00%
Sell (S)	Returns expected to significantly underperform the sector average over 12 months.	0.00%	0.00%	0.00%

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