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EQUITY RESEARCH
Company Report

November 4, 2015

Isis Pharmaceuticals (ISIS - $ 51.27)

Healthcare/Biotechnology

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

ISIS-TTR$_{Rx}$ Updates: Physician-Sponsored Phase II Study and FAC / wt-TTR Amyloidosis Phase III Trial Design

Yesterday, ISIS updated investors on ISIS-TTR$_{Rx}$ in FAP/wt (wild type)-TTR amyloidosis development. It included an interim analysis of an open label Phase II study and the study design of the Phase III trial in FAC/wt-TTR amyloidosis, to start in 1H16 by GlaxoSmithKline (GSK).

- **Phase II study results encouraging.** Preliminary Phase II results from the study by Dr. Merrill D. Benson indicated that ISIS-TTR$_{Rx}$ treatment stabilized cardiac disease. Specifically, the interventricular septum thickness (IVS) of treated patients (n=3) has decreased 1.9% from the baseline ($\geq$1.3 cm) after one year of therapy, while that of untreated patients increased 14% according to a prior natural history study (n=5). IVS thickness is measured by MRI. An expert indicated that IVS $\geq$1.3 cm correlates with the overall survival outcome. If such patients are not adequately treated, death could be imminent in 5 years. Two studies support this notion (see next page for citations). Despite the patient size of study is small, we remain encouraged by the positive trends of several analyses from the study (see next page).
- **Phase III trial design.** The Phase III (CARDIO-TTR) trial is a randomized, double-blind, placebo controlled study that intends to enroll wt-TTR amyloidosis and FAP patients (n=500). ISIS did not reveal the patient size breakdown between the two indications. Patients will receive a weekly dose of either 300mg ISIS-TTR$_{Rx}$ or placebo for two years and followed with an open label extension study. The primary endpoint is a clinical composite outcome of mortality, cardiac transplant, and cardiovascular hospitalization. The trial will start in 1H16 by GSK. Data will be assessed in combined and in separated patient groups. Both indications are under-diagnosed and patients are elderly and fragile. Although with higher clinical risk than a functional test such as 6MWD, a clinical study with MACE type endpoint, if successful, could afford a much robust package that could gain greater acceptance by patients, payers and doctors, in our opinion. GSK is scheduled to run a Phase III FAP study in Japan in 2016.
- **Action.** We are reiterating our Buy rating and $75 target price to reflect our bullish view on progress in ISIS's pipeline, especially ISIS-APOCIII$_{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 (11/03/2015)	$ 51.27
52–Week High (3/20/2015)	$ 77.80
52–Week Low (9/29/2015)	$ 37.38
Market Cap. (MM)	$ 6,150
Shares Out. (MM)	120

Earnings Estimates: (per share)

(Dec)	1Q	2Q	3Q	4Q	FY	P/E
FY-15E	-0.14A	0.30	-0.28	-0.38	-0.50	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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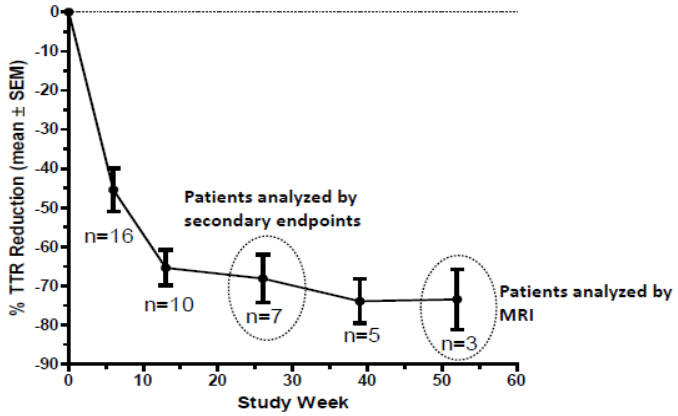
- **Two supporting studies of low survival prospect in FAC / wt-TTR amyloidosis patient:** 1) Ruberg, F.J. *et. al.* (Am Heart J, 2012, 164: 222-228) indicated that the median survival from diagnosis was 25.6 months for ATTRm and 43 months for wt-TTR amyloidosis (n=29); and 2) Connors, L.H. *et. al.* (J. of Protein Folding Disorders, 2011 18:sup1, 157-159) showed median survival was 4.3 years for wt-TTR amyloidosis (n=82) and varies (41 – 62 months) for FAP of different mutations (n=96).
- **More details of open label Phase II (ATTR-CM) study.** It is a single center (Indiana University), open label Phase II study that designed to evaluate ISIS-TTR$_{Rx}$ (300mg, once weekly for 2 years) in a mixed FAC and wt-TTR patients (n= 20 with`50% each). The study showed a sustained TTR reduction (Figure 1) and various cardiac metrics analyses, including 6MWD (Figure 2).

Figure 1: TTR reduction in of ATTR-CM study



Source: Company presentation

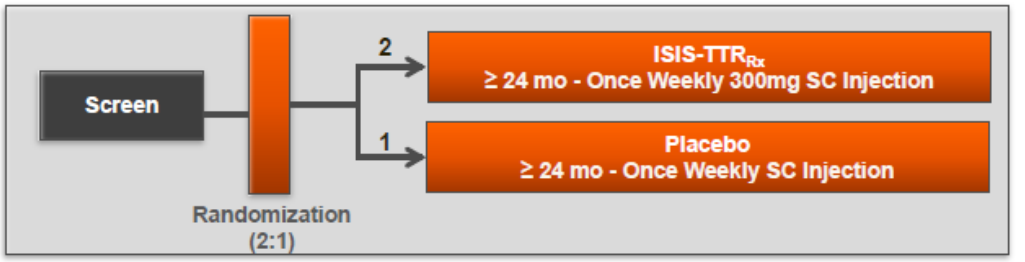
Figure 2: Results of multiple secondary endpoints of ATTR-CM study

Endpoint	ISIS-TTR$_{Rx}$ Treated Patients Mean (SEM) at Each Visit			Mean (SEM) Change from Baseline
Measurement	Baseline (N=7)	6 Months (N=7)	12 Months (N=3)	12 months* (N=3)
BNP (pg/mL)	350 (71)	309 (65)	265 (43)	-107 (64)
6MWT (ft)	1252 (196)	n/a	1517 (100)	36 (127)
IVS (cm)	2.1 (0.2)	2.0 (0.2)	2.0 (0.2)	0.1 (0.03)
LVPW** (cm)	2.0 (0.2)	2.0 (0.2)	1.7 (0.2)	0.1 (0.1)
Strain (global)	-11.3 (1.1)	-11.2 (1.1)	-12.1 (1.9)	1.4 (1.2)

*Mean (SEM) - changes calculated from baseline to month 12 for each individual
**Left Ventricular Posterior Wall

Source: Company presentation

Figure 3: CARDIO-TTR Phase III study design



Source: Company presentation

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Anticipated milestones in 2015 and beyond

Product	Indication	Event	Timing	Importance
ISIS-APOCIII$_{Rx}$ (Volanesorsen)	Familiar chylomicronemia syndrome (FCS)	Report of Phase III study top-line results	**1Q17**	****
	Familiar partial lipodystrophy	Commencement of Phase III study	**4Q15**	***
		Report of Phase III study top-line results	**Late 2017**	****
ISIS-SMA$_{Rx}$	Spinal muscular atrophy (infant)	Report of Phase III study top-line results	**1H17**	****
	Spinal muscular atrophy (children)	Report of Phase III study top-line results	**1H17**	****
ISIS-TTR$_{Rx}$	Familiar amyloidosis polyneuropathy (FAP)	Completion of patient recuritment of Phase II/III study	**4Q15**	***
		Commence Phase III study in Japan	**2016**	***
		Report of Phase II/III study top-line results	**1H17**	****
		Filing of NDA	**2H17**	***
		Report of interim analysis of ALN-TTR$_{IV}$ Apollo Phase III study by ALNY	**2017/2018**	***
		Potential approval	**2018**	****
	Familiar amyloidosis cardiomyopathy (FAC)/wt-TTR	Potential to start Phase II/III study	**1H16**	***
		Additional updates	**2016, 2017**	***
ISIS-FXI$_{Rx}$	Clotting disorders	Report Phase II in atrial fibrillation of end-stage kidney disease patient study data	**2H16**	****
		Potential to start Phase III study	**2H16/2017**	***
ISIS-APOCIII-L$_{Rx}$	Severely high triglyceride	Start Phase I study	**1Q16**	***
ISIS-DMPK-2.5$_{Rx}$	Myotonic dystrophy 1	Report Phase II proof-of-concept study data	**1H16**	****
ISIS-PKK$_{Rx}$	Hereditary angioedema	Start Phase II study	**1H16**	***
		Potentially report Phase II study top-line results	**2017**	****
ISIS-FGFR4$_{Rx}$	Obesity	Possibly report Phase II study	**2016 / 2017**	***
ISIS-DGAT2$_{Rx}$	NASH	Start I study	**2H15**	**
ISIS-HTT$_{Rx}$	Huntington disease	Report Phase I/II study top-line results	**2016**	**
ISIS-GCGR$_{Rx}$	Diabetes	Start dose optimizing study	**2H15**	**
ISIS-GCCR$_{Rx}$		Make decision for the next step	**2H15**	***
	Cushing's syndrome	Make decision for the next step	**2H15**	***
ISIS-ANGPTL3$_{Rx}$	Severe hyperlipidemia	Start Phase I study	**4Q15**	***
ISIS-APO(a)$_{Rx}$	Severe high Lipoprotein(a)	Report Phase II study results	**4Q15**	***
ISIS-APO(a)-L$_{Rx}$	Severe high Lipoprotein(a)	Data Phase I study	**4Q15**	***
ISIS-BIIB3$_{Rx}$	Neurodegenerative disease	Start Phase I study	**4Q15**	**
ISIS-GSK4$_{Rx}$	Ocular disease	Start Phase I study	**1H16**	**
ISIS-HBV$_{Rx}$	HBV	Initiate Phase II study	**1H16**	***
		Potentially report Phase II study top-line results	**2H16**	****
ISIS-STAT3-2.5$_{Rx}$	DLBCL	Potentially to start PD1 (MEDI4736) combination Phase II study	**4Q15**	***
RG-101	HCV	Report Phase II study results	**4Q15**	***
		Report combo Phase II study results	**2016**	***
ISIS-AR$_{Rx}$	Prostate cancer	Report Phase I/II study results	**2H15**	***

***** / ***** 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

($'MM)	2012	2013	2014	1Q15	2Q15	3Q15E	4Q15E	2015E	2016E	2017E	2018E	2019E	2020E
Revenue													
Kynamro profit share								0.0	3.7	16.8	26.0	34.7	40.3
ISIS-TTR$_{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	119.7	53.8	45.7	281.1	235.5	244.9	249.8	244.8	235.0
Licensing and royalty revenue	5.6	3.1	11.6	0.7	0.8	1.1	1.0	3.6	3.3	3.3	3.4	3.4	3.4
Total revenue	102.0	147.3	214.2	62.6	120.4	54.9	46.7	284.6	242.4	308.5	491.9	778.1	1,057.9
Research and development	158.5	184.0	241.8	64.4	68.0	71.4	75.0	278.8	301.1	322.2	338.3	351.9	365.9
General and administrative	12.5	14.9	20.1	7.5	7.8	7.9	8.2	31.3	32.3	35.2	38.4	41.8	45.1
Total Operating Expenses	171.0	199.0	261.9	71.9	75.8	79.3	83.1	310.2	333.4	357.4	376.7	393.7	411.1
Operating Incomes (losses)	(68.9)	(51.7)	(47.7)	(9.3)	44.6	(24.4)	(36.4)	(25.6)	(91.0)	(48.9)	115.2	384.5	646.8
Equity in net loss of Regulus Therapeutics Inc.	(1.4)	0.0											
Investment income	1.8	2.1	2.7	0.8	0.9	0.9	0.9	3.6	4.0	4.4	4.8	5.3	5.8
Interest expense	(21.2)	(19.4)	(22.2)	(9.0)	(9.1)	(9.1)	(9.1)	(36.4)	(37.5)	(41.2)	(45.4)	(49.9)	(49.9)
Gain on investments, net	1.5	2.4	1.8	-	0.0	0.0	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)	(32.8)	(31.6)	(56.9)	(16.6)	(71.6)	(71.1)
Income before tax	(74.6)	(66.6)	(54.4)	(17.5)	36.4	(32.6)	(44.7)	(58.4)	(122.7)	(105.8)	98.7	312.8	575.7
Tax	9.1	5.9	15.4	0.8	(0.8)	(1.0)	(1.0)	(2.0)	5.7	0.0	(36.5)	(115.7)	(213.0)
Net Income (Loss) GAAP	(65.5)	(60.6)	(39.0)	(16.7)	35.6	(33.6)	(45.7)	(60.4)	(117.0)	(105.8)	62.2	197.1	362.7
Net Income (Loss) Applicable to Common Shareholders	(65.5)	(60.6)	(39.0)	(16.7)	35.6	(33.6)	(45.7)	(60.4)	(117.0)	(105.8)	62.2	197.1	362.7
Net Earnings (Losses) Per Share—Basic and Diluted	($0.65)	($0.55)	($0.33)	($0.14)	$0.30	($0.28)	($0.38)	($0.50)	($0.96)	($0.86)	$0.50	$1.55	$2.80
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	127.8	119.7	120.1	121.7	123.7	125.7	127.7	129.7	131.7
Margin Analysis (% of Sales/Revenue)													
Costs of goods									0%	0%	0%	0%	0%
R&D	155%	125%	113%	103%	56%	130%	161%	98%	124%	104%	69%	45%	35%
MG&A	12%	10%	9%	12%	6%	14%	17%	11%	13%	11%	8%	5%	4%
Operating Income (loss)	-68%	-35%	-22%	-15%	37%	-45%	-78%	-9%	-38%	-16%	23%	49%	61%
Net Income	-64%	-41%	-18%	-27%	30%	-61%	-98%	-21%	-48%	-34%	13%	25%	34%
Financial Indicator Growth Analysis (YoY%)													
R&D revenue under collaborative agreements	0%	50%	40%	217%	111%	23%	-45%	39%	-18%	4%	2%	-2%	-4%
Licensing and royalty revenue	95%	-45%	277%	-92%	72%	315%	-57%	-69%	-8%	2%	1%	0%	0%
Total Revenue	3%	44%	45%	122%	111%	25%	-45%	33%	-15%	27%	59%	58%	36%
R&D	1%	16%	31%	21%	15%	17%	10%	15%	8%	7%	5%	4%	4%
SG&A	-2%	19%	35%	70%	74%	77%	20%	56%	3%	9%	9%	9%	8%
Operating Loss	-3%	-25%	-8%	-69%	-771%	14%	-462%	-46%	256%	-46%	-336%	234%	68%
Total Other Income, net	-59%	163%	-55%	110%	80%	117%	-248%	393%	-4%	80%	-71%	332%	-1%
Net Income	-23%	-7%	-36%	-47%	-395%	26%	-247%	55%	94%	-10%	-159%	217%	84%
EPS	-23%	-16%	-40%	-47%	-391%	24%	-245%	52%	91%	-11%	-158%	212%	81%

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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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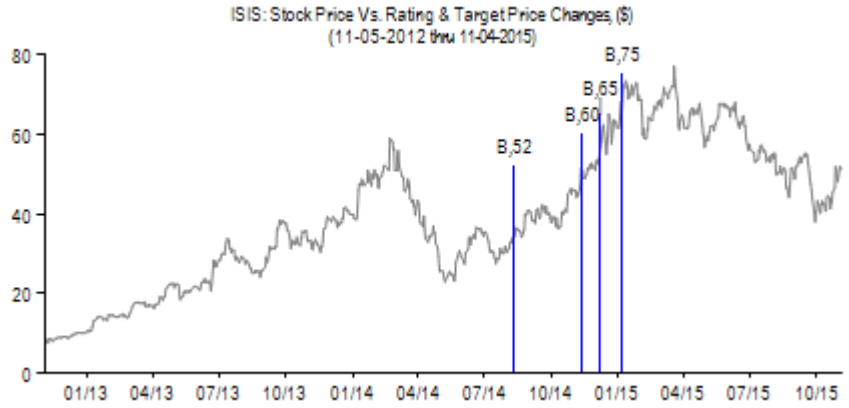
RATINGS INFORMATION

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**

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			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%	28.13%	6.25%
Hold (H)	Expected returns to be in line with the sector average over 12 months.	3.13%	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

GlaxoSmithKline, (GSK – Not Rated)

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