Global Equity Research

UBS Warburg

**December 6, 2002** | **Biotechnology** | **United States**

# Isis Pharmaceuticals Inc (ISIS)[1,37,81]

**Reduce**

## Key Statistics

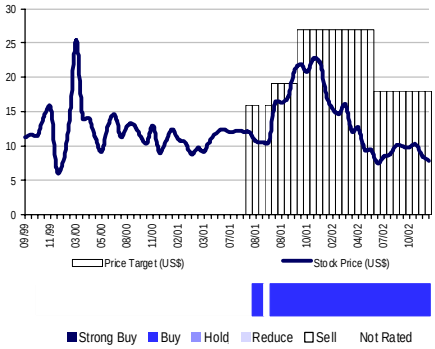
| | |
|---|---|
| **Price** | $7.91 |
| **52-Wk Range** | $23-7 |
| **Price Target** | $6.00 |
| **Return Pot'l.** | (24.1%) |
| **Mkt. Cap(MM)** | $436 |
| **Sh. Out.(MM)** | 55.1 |
| **Float** | 85% |
| **Inst. Hldgs.** | 53.1% |
| **Avg. Volume(K)** | 636 |
| **Curr.Div./Yield** | None/NA |
| **Sec.Grwth.Rate** | 34% |
| **Convertible?** | Yes |
| **Debt/Capital** | 111.0% |
| **ROE LTM** | (49.9%) |
| **Book Value/Share** | $2.85 |
| **Price/Book** | 2.8x |

## Quarterly Earnings Per Share (fiscal year ends December)

| | 2001A | 2002E | *Prev* | 2003E | *Prev* |
|---|---|---|---|---|---|
| **1Q** | ($0.58) | ($0.34)A | | | |
| **2Q** | (0.58) | (0.35)A | | | |
| **3Q** | (0.29) | (0.41)A | | | |
| **4Q** | (0.31) | (0.36) | | | |
| **Year** | **($1.70)** | **($1.46)** | | **($1.38)** | |
| **FC Cons.:** | ($1.70) | ($1.45) | | ($1.21) | |
| **P/E:** | NM | NM | | NM | |
| **Revs.(MM):** | $53 | $80 | | $79 | |
| **P/Rev.:** | NM | NM | | NM | |
| **EBITDA(MM):** | ($46) | ($54) | | ($57) | |

ISIP is a biopharmaceutical company focused on the development of genomics based antisense molecules for the oncology and inflammatory markets.

Source: UBS Warburg LLC and First Call consensus estimates




## ISIS Pharma: Downgrade to Reduce Ahead of Affinitac Data

### Summary

- We are downgrading the shares of ISIS to Reduce from Buy.
- Our downgrade reflects heightened concern regarding the impending release of phase III data for Affinitac. Recent conversations with investigators involved in the trial have not supported or increased our confidence about a successful outcome to this trial.
- Affinitac is being tested in a 600 patient phase III trial for the treatment of non-small cell lung cancer (NSCLC). We expect the data to be released during 1Q03.

### Action

- While we recognize the difficulties in drawing conclusions from anecdotal conversations with investigators, we cannot ignore the recent spat of unpromising updates that we have received. As such, we can no longer recommend investors buy ISIS shares, particularly ahead of a near-term event that will likely have a dramatic effect on ISIS shares.
- Given our view that the likelihood of a positive outcome has somewhat declined, we believe a Reduce rating is appropriate; we will revisit our rating upon the release of the phase III data.


**Andrew Gitkin**
+1-212-713 2611
andrew.gitkin@ubsw.com
**Brendan Boylan, Associate Analyst**
+1 212 713 2717
brendan.boylan@ubsw.com


**Companies mentioned and disclosures on page 4**

## Valuation

- If the data are positive, we believe ISIS shares could trade to the mid-teen range; likewise, if the data are not positive, we believe shares could trade down to the $4-6 range (keeping in mind the $2/share in net cash). While it is difficult to say, we currently believe that there is a 60%-70% chance of a negative outcome. These expectations yield a risk-adjusted weighted average stock price target of roughly $6/share. As such, we are lowering our price target to $6/share from $18/share to reflect our cautious posture on the outcome of this event. Our $6/share price target is based upon a 26x multiple on 2007 EPS of $0.95, discounted back at 40% per year. Our new price target utilizes the same methodology as our previous target, however we have increased our discount rate to reflect the added risk to our 2007 earnings estimate.

## Additional Information

***Rationale for Downgrade -*** We are downgrading the shares of ISIS to Reduce from Buy. Our downgrade reflects heightened concern regarding the impending release of phase III data for Affinitac. Recent conversations with investigators involved in the trial have not supported or increased our confidence about a successful outcome to this trial. While we recognize the difficulties in drawing conclusions from anecdotal conversations with investigators, we cannot ignore the recent spat of unpromising updates that we have received. As such, we can no longer recommend investors buy ISIS shares, particularly ahead of a near-term event that will likely have a dramatic effect on the stock price. Given our view that the likelihood of a positive outcome has somewhat declined, we believe a Reduce rating is appropriate; we will revisit our rating upon the release of the phase III data.

***Phase III Data Expected in 1Q03 -*** ISIS and its corporate partner, Eli Lilly (LLY), are currently conducting two phase III studies of Affinitac (ISIS 3521) for the treatment of non-small cell lung cancer (NSCLC). Data for the initial 600 patient ISIS-sponsored study are expected to be released during 1Q03. This study is examining patients receiving carboplatin + Taxol versus carboplatin + Taxol + Affinitac in patients with front-line lung cancer. The second study, which is being sponsored by ISIS' partner LLY, is enrolling 1,000 patients; data is expected in early-2004. This study has three arms: 1) gemcitabine + cisplatin +/- Affinitac; 2) docetaxel +/- Affinitac; and 3) carboplatin + Taxol +/- Affinitac in front line lung cancer. Historical median survival with standard treatment of carboplatin + Taxol is 8.1 months; we believe ISIS and LLY will need to demonstrate a minimum 30% survival benefit (11-12 months) to receive an approval from the FDA in this indication.

***Data Release Will Be A Major Validating Event for Antisense Technology -*** Given the still unproven nature of antisense from a clinical standpoint, particularly in large indications such as NSCLC, investors will likely scrutinize the upcoming Affinitac data. We believe that the phase III data release will be one of the primary validating events for antisense technology (the other event likely being the release of phase III data for Genta's Genasense, which is also in phase III trials). Indeed, concerns amongst the research and clinical community continue to linger regarding the clinical utility of antisense; namely, can antisense be an effective therapy. Specifically, concerns regarding bioavailability, dosing levels (getting enough drug into cancer cells to inhibit mRNA), dosage frequency and administration. While 2$^{nd}$ generation antisense technology appear able to address some of these concerns, investors are still exposed to 1$^{st}$ generation technology in the near-term. Currently, the lead 2$^{nd}$ generation antisense candidates are only in Phase II studies. As such, we believe it is appropriate to view the upcoming data release for Affinitac as somewhat of an industry wide "acid test" for antisense (at least until 2$^{nd}$ generation technology advances into phase III trials).

Therefore, we believe the release of the phase III Affinitac data will likely create a significant amount of volatility in ISIS shares (positive or negative), as investors use the data as a benchmark to judge the viability of antisense as a therapeutic intervention. Given the company's extensive antisense patent estate (more than 1,000 antisense patents) and its robust pipeline of antisense drugs (5 currently in clinical trials for 9 indications), ISIS has the most to gain, and lose, depending on the outcome of the trial.

***Insight into Phase III Data Appear Unpromising….*** The basis for our downgrade stems from recent conversations from several trial investigators. Recall that the trial is open labeled due to the manner in which the drug is administered (via an implantable catheter). As such, investigators (and patients) know who has, and who has not received drug. Thus, comments gained from conversations with investigators are more relevant (given their knowledge of patient outcomes by drug or not) versus typical blinded studies in which investigators do not know who is, and isn't, receiving drug. While we certainly recognize the difficulty of extrapolating the outcome of the whole trial from such conversations, suffice to say that we received enough feedback to make us appropriately comfortable in changing our investment rating. For the trial to be a success, we believe Affinitac will need to generate a 30% median survival benefit over the control group; this should translate into a median survival of roughly 10-12 months based upon historical survival rates. In our conversations, we did not gain a sense that there was a meaningful difference in survival between the Affinitac and control group. Indeed, in all our conversations, not once did someone mention that they were seeing a treatment effect relative to the control group (despite some patients achieving median survival of 12 months). Given this we cannot recommend investors to continue accumulating shares of ISIS ahead of this major, stock moving event.

***Risk Now Outweighs the Reward -*** We recognize that downgrading to a Reduce may be a bit cautious on our part given the difficulties in extrapolating investigator conversations to overall trial outcomes, but we nonetheless still believe it is appropriate given the recent anecdotes and the significance of the phase III data to ISIS valuation. We have always noted that ISIS is a risky investment given its dependence on antisense; a technology that has yet to have a major clinical success. However, given its exhaustive patent position, its compelling phase II data for Affinitac, a robust pipeline and its landmark deal with Eli Lilly (and other notable partners like Amgen, Merck and Chiron), we had previously believed that a Buy rating was warranted. However, recent conversations have tilted our sentiment to a more cautious position regarding Affinitac, so much so that we believe a Reduce rating is appropriate in the near-term.

## Statement of Risk

- There are a number of risks inherent in investing in the biotech industry. These include, but are not limited to, clinical trial failures, capital restrictions, and failure to achieve significant revenues and earnings, as well as other unforeseen events. Any investment should carefully weigh all aspects of the company's product portfolio and financial position in relation to any upside potential.

## Global ratings: Definitions and allocations

| UBS rating | Definition | Rating category[1] | Coverage[2] | IB services[3] |
|---|---|---|---|---|
| Strong Buy | Greater than 20% excess return potential; high degree of confidence | Buy | 53% | 40% |
| Buy | Positive excess return potential | | | |
| Hold | Low excess return potential; low degree of confidence | Hold/Neutral | 42% | 26% |
| Reduce | Negative excess return potential | | | |
| Sell | Greater than 20% negative excess return potential; High degree of confidence | Sell | 5% | 18% |

Excess return: Target price / current price – 1 + gross dividend yield – 12-month interest rate. The 12- month interest rate used is that of the company's country of incorporation, in the same currency as the predicted return.

1: UBS Strong Buy and Buy = Buy; UBS Hold = Hold/Neutral; UBS Reduce/Sell = Sell.

2: Percentage of companies under coverage globally within this rating category.

3: Percentage of companies within this rating category for which investment banking (IB) services were provided within the past 12 months.

Source: UBS AG, its subsidiaries and affiliates; as of 30 September 2002.

## Companies Mentioned

| Company Name | Ticker | Price | Company Name | Ticker | Price |
|---|---|---|---|---|---|
| **Eli Lilly & Co**[81] | LLY | $67.07 | **Genta Inc**[1,37] | GNTA | $10.36 |
| **Isis Pharmaceuticals Inc**[1,37,81] | ISIS | $7.91 | | | |

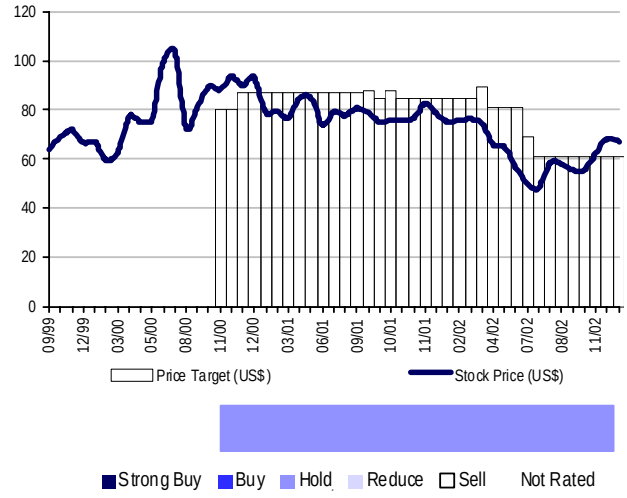
Price quoted on December 5, 2002 Source: UBS Warburg

1. UBS Warburg LLC and/or one of its affiliates makes a market in the securities and/or ADRs of this company.

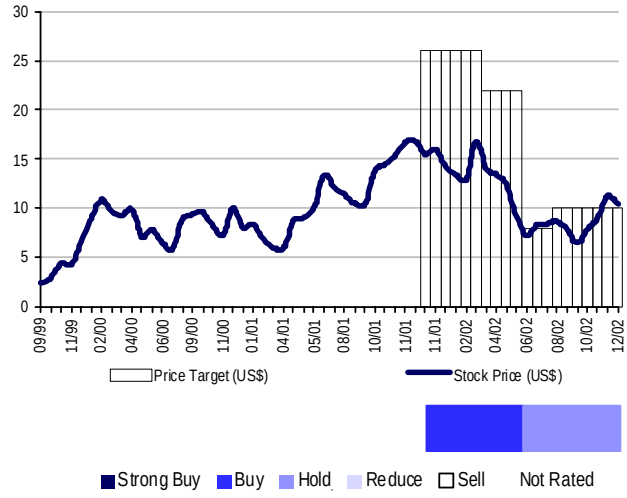
37. Within the past 12 months, UBS AG, its affiliates or subsidiaries has received compensation for investment banking services from this company.

81. UBS AG, its affiliates or subsidiaries has acted as manager/co-manager in the underwriting or placement of securities of this company or one of its affiliates within the past 12 months.

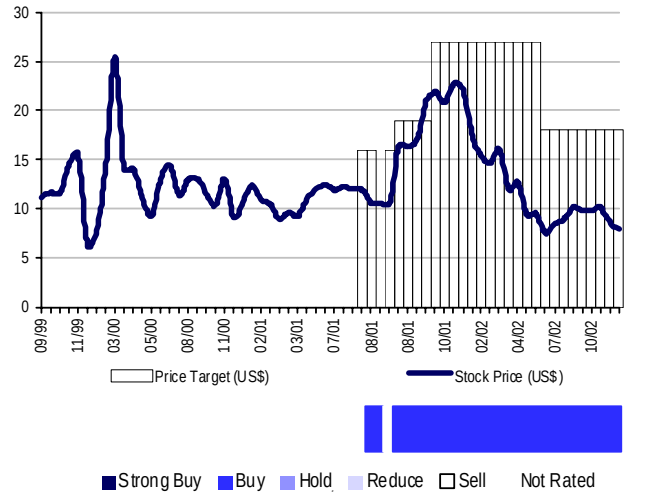
### Eli Lilly & Co (US$)




### Genta Inc (US$)



## Isis Pharmaceuticals Inc (US$)




Source: UBS AG, its subsidiaries and affiliates; as of Thursday, December 05 2002

Unless otherwise indicated, please refer to the Valuation and Risk sections contained within the body of this report.
For a complete set of disclosure statements associated with the companies discussed in this report, including information on valuation and risk, please contact UBS Warburg LLC, 1285 Avenue of Americas, New York, New York, 10019, Attention: Publishing Administration.

**UBS Warburg LLC, 1285 Avenue of the Americas, New York, NY 10019 Phone: +1-212-713-2000**