Ironwood Pharmaceuticals

Compelling Linaclotide Data from First IBS-C Trial; Reiterate Overweight - ALERT

Overweight

IRWD, IRWD US
Price: $9.74

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US Biotechnology

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Ironwood and partners Forest/Almirall reported impressive positive top-line data from the first of the two phase 3 trials (study ’31) of linaclotide in irritable bowel syndrome with constipation (IBS-C). Linaclotide met all 16 primary and secondary endpoints, including abdominal pain, which is a very difficult hurdle to hit. Ultimately, meeting both the pain and complete spontaneous bowel movement (CSBM) endpoints bodes well for commercial success given significant market differentiation for both IBS-C and chronic constipation (CC). With the ’31 data in hand, we are quite comfortable with the probability of success for the second of the two pivotal studies in IBS-C (study ’302; data in 4Q10). This is largely driven by the fact that the abdominal pain benefit improves over time, which could help the longer-duration ’302 study. In terms of timelines and next steps, the NDA filing is expected by mid-2011, and ultimately final data from both phase 3 studies could be presented at the Digestive Disease Week meeting (May 7-10, 2011; Chicago). Overall, the consistency of the CC and IBS-C data in phase 2 and phase 3 studies, along with a very clean safety profile, gives us confidence in US and EU approval and helps support our peak potential of $3B in the US alone. We are reiterating our Overweight rating on IRWD shares.

- **Linaclotide meets all primary/secondary endpoints and, importantly, the abdominal pain endpoint.** Linaclotide met all four coprimary endpoints with statistical significance for US approval, which included two composite endpoints of complete spontaneous bowel movement (CSBM) and pain (12.1% vs. 5.1%, p=0.0004 for 9/12 weeks and 33.6% vs. 21%, p<0.0001 for 6/12 weeks). On the two solitary endpoints, the data looked strong as well (pain, 34.3% vs. 27.1%, p=0.0262 for 9/12 weeks and CSBM 19.5% vs. 6.3%, p<0.0001 for 9/12 weeks). Additionally, linaclotide met the criteria for EU approval by hitting 12-week abdominal pain/abdominal discomfort responder (55% versus 42%; p=0.0002) and 12-week IBS degree of relief responder (37% versus 18%, <0.0001). We believe the abdominal pain benefits observed in this study are clinically significant given that pain is a hallmark of IBS-C. This is supported by multiple discussions with KOLs in the GI field.

- **Rapid onset of action and sustained benefit confirmed.** Improvements in abdominal pain and CSBMs were observed within the first week and sustained over the 12-week treatment (16 weeks in some patients). This was also confirmed in the randomized withdrawal period, in which placebo patients switched to linaclotide observed a similar benefit. We believe rapid onset of action and sustained benefit could be key commercial differentiators.

- **No real safety surprises.** The most frequent adverse event (AE) in the treatment arm was diarrhea (19% vs. placebo 4%), with the majority being mild/moderate in severity (17%). Indeed, 6% of patients discontinued linaclotide due to diarrhea (0.3% for placebo). Based on our conversation with Ironwood, the diarrhea symptoms were mostly observed in the first month of treatment and improved over time. Overall, the AE profile is in line with previous linaclotide studies and doesn’t look problematic. There are two safety studies ongoing (n~2,500) which should further support the profile.

See page 3 for analyst certification and important disclosures.

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- **Second phase 3 study in IBS-C expected 4Q; NDA filing expected mid-2011.** We have increased confidence in the success of the second phase 3 trial in IBS-C, based on today's results. We expect linaclotide to show a sustained benefit over 26 weeks in study '302, which could be important for a chronic IBS-C label (study '31 duration of 12 weeks). Importantly, the pain benefit in study '31 improved over time, which is a good indicator of significant benefit, and should bode well for the longer '302 trial. NDA filing for both CC and IBS is on track for mid-2011. Recall, linaclotide has already demonstrated favorable efficacy and safety in phase 3 CC trials across all endpoints. Should the second phase 3 IBS-C be similar to the first, we see a high probability of ultimate approval in the US and EU.

- **Reiterate Overweight rating.** We believe positive data from the first of two phase 3 trials of linaclotide support use in IBS-C and confirm improvement in abdominal pain as a key differentiating factor. These data further increase the probability of a positive outcome from the similarly designed second phase 3 trial (study '302; top-line data in 4Q), in our view. Hence, we reiterate our Overweight rating on IRWD shares.

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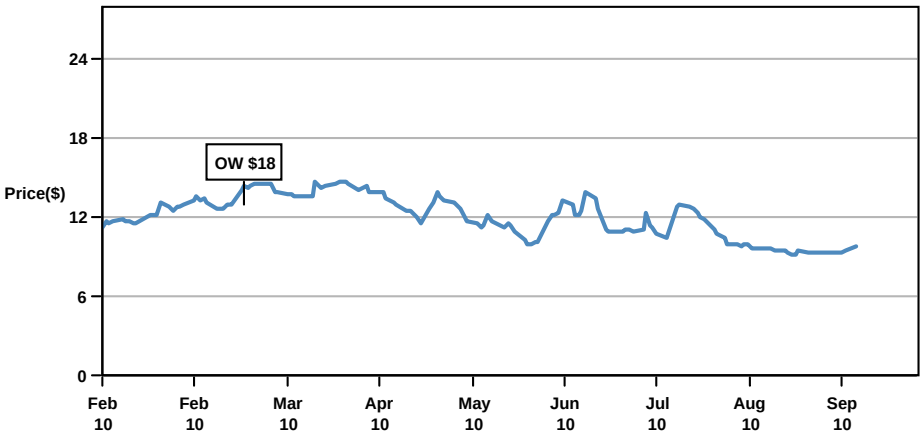
Ironwood Pharmaceuticals (IRWD) Price Chart



Date	Rating	Share Price ($)	Price Target ($)
15-Mar-10	OW	12.91	18.00

Source: Bloomberg and J.P. Morgan; price data adjusted for stock splits and dividends.
Initiated coverage Mar 15, 2010. This chart shows J.P. Morgan's continuing coverage of this stock; the current analyst may or may not have covered it over the entire period.
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