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Stock Rating
Overweight

Industry View
In-Line

Initiation

Ironwood Pharmaceuticals

Blockbuster Opportunity with Near-Term Catalyst

We are initiating coverage of IRWD with an Overweight rating and $19 price target. Ironwood has a Phase III drug, linaclotide, being developed for chronic constipation (CC) and irritable bowel syndrome with constipation (IBS-C). We see a high chance of clinical and regulatory success as well as blockbuster sales potential for linaclotide, which is likely to be the first IBS-C drug with a significant pain benefit. Investors overestimate clinical trial risk and underestimate the potential in IBS-C, in our opinion. Key potential catalysts are: 1) Phase III IBS-C data (2H10); 2) IBS-C & CC NDA filing (1H11); 3) linaclotide approval (late '11/early '12).

Key Debates: 1) Will linaclotide show a benefit in treating abdominal pain in Phase III IBS-C trials? 2) How big can the drug be in IBS-C? 3) Will chronic constipation prove to be a real market? 4) How and when will Ironwood build a pipeline beyond linaclotide?

Why we are optimistic: Previous data have been convincing that linaclotide works in IBS-C, and we see a high probability of Phase III success in both the composite IBS-C endpoint and treating pain. We expect linaclotide will take share from current drugs because of its efficacy, and more importantly, bring more patients in for treatment. Our peak linaclotide estimates for IBS-C in the US ($850mn+) and WW (~$1.2 bn) are higher than consensus.

Key factors beyond IBS-C: 1) Linaclotide has positive Phase III data in CC, which we view as adequate for approval. We (and investors) are generally less optimistic on the commercial opportunity in CC given a variety of over the counter options. Our bull case outlines the value (~$28/share) if Ironwood is successful in CC, which could lead to peak linaclotide sales of $2 bn+. **2)** Ironwood does not have a pipeline beyond linaclotide; long-term returns will depend on the company's ability to invest cash flows wisely.

Key Ratios and Statistics

Reuters: IRWD.O Bloomberg: IRWD US
Biotechnology / United States of America

Price target	**$19.00**
Shr price, close (Mar 12, 2010)	$12.91
Mkt cap, curr (000s)	$1,258,294,688
52-Week Range	$13.58-11.20

Fiscal Year ending	**12/09**	**12/10e**	**12/11e**	**12/12e**
ModelWare EPS ($)	**(0.66)**	**(0.57)**	**(0.47)**	**(0.54)**
P/E	**NM**	**NM**	**NM**	**NM**
Cash and cash eq ($mm)	82,218	209,611	147,468	204,479

Unless otherwise noted, all metrics are based on Morgan Stanley ModelWare framework (please see explanation later in this note).
e = Morgan Stanley Research estimates

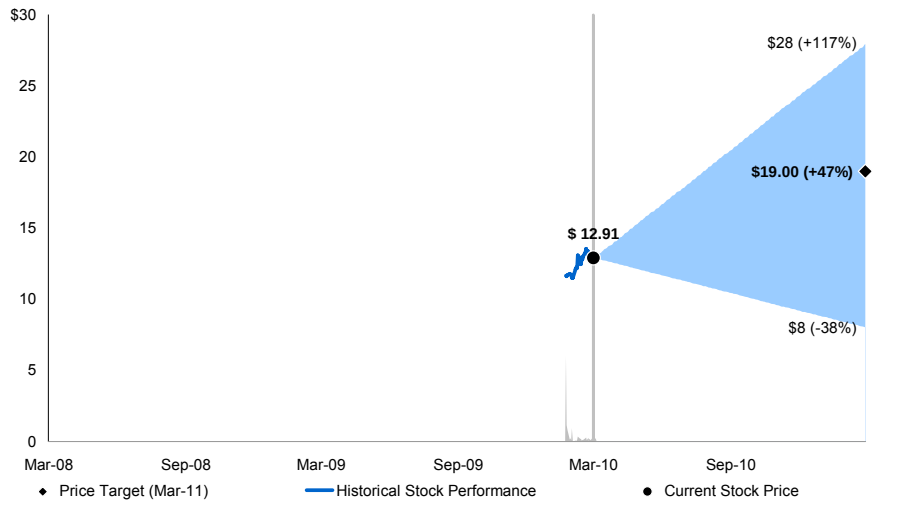
Key Investment Debates:

DEBATE	MARKET'S VIEW	OUR VIEW
Will Phase III data for linaclotide in IBS-C show a benefit in treating pain?	The market is generally optimistic that linaclotide improves constipation given myriad positive datasets across two different indications. However, views on the drug's ability to improve pain scores are more mixed. Phase II data were positive on pain improvement, but many are concerned that: 1) the pain scale changed between Phase II (5 point scale) and Phase III (11 point scale); and 2) pain is a subjective endpoint that has failed for a number of solid drugs which later proved quite efficacious on the measure.	We are optimistic linaclotide will show a clear benefit on pain in Phase III trials as: 1) all data seen to date (Phase IIb IBS-C and Phase III CC) suggest pain improvement (Phase II trial showed 47% reduction in pain score vs. 26% in the placebo arm); 2) we are comfortable with the eleven point scale as prior trials suggest a higher sensitivity than the five point scale; and 3) the drug's mechanism provides a scientific rational as to why linaclotide can reduce pain. We believe positive Phase III data in treating **both** the constipation and the pain associated with IBS-C will be the key catalyst for IRWD in 2010. *Where we could be wrong: The bar for success in the Phase III IBS-C trial is high, with patients needing to show a benefit on this novel pain score (FDA requested change) in 9 of 12 weeks of treatment. Pain remains one of the less predictable clinical trial endpoints, and while we do not believe it is essential for regulatory success, a lack of a pain benefit would lead us to decrease our peak sales estimates in IBS-C by 30-50%.*
While clearly a real market, what penetration is reasonable in IBS-C?	Many investors focus on peak sales for Novartis' Zelnorm prior to its removal from the market (~$500 mn WW) and current sales for Takeda's Amitiza (~$200 mn). Additionally, launches into new primary care categories are difficult to predict and increasingly slow. In addition, the Street is pessimistic about the potential of the drug in Europe and Almirall, Ironwood's EU partner for linaclotide, will use this drug to build its pan-European infrastructure, increasing execution risk.	We believe linaclotide has shown a profile to date that will lead to >$1bn in WW peak sales in IBS-C. The key will be improvement in abdominal pain in Phase III, as our diligence suggests this is greatest area of unmet need with current therapies. Takeda's Amitiza has faltered to date because of its side effect profile (high rates of nausea) as well as limited efficacy (overall and more specifically in dealing with abdominal pain). Linaclotide has better efficacy and tolerability than any agent in this disease to date and our peak penetration estimates remain relatively conservative at <5% of IBS-C population (40-45% of patients unsatisfied with current treatments). *Where we could be wrong: The track record for prescription drugs in IBS-C and CC is not great. The modest efficacy and side effects of other prescription agents and Zelnorm's prior withdrawal from the market may have a greater hold on the physician base than we estimate and physicians may hesitate to adopt a new drug in this area. Also, there are competitors 3-4 years behind in development, and we may be underestimating competitive risks.*

DEBATE	MARKET'S VIEW	OUR VIEW
Will chronic constipation develop into a real market?	Investors are skeptical that chronic constipation will develop into a significant market. There are numerous over-the-counter (OTC) alternatives, payers are likely to resist reimbursement, and physicians do not view chronic constipation with the same urgency as many other markets.	We are more or less in line with consensus, and despite a significantly greater addressable market than IBS-C (in US, 30 mn vs. 11 mn), we expect peak sales will be demonstrably lower. In addition, patients with CC tend to have less pain and discomfort than IBS-C patients, thus the desire for therapy is less urgent and duration of therapy may be limited. We are intrigued by management's attempt to alter the physician dialogue around this disease – "constipation and discomfort/pain refractory to OTC drugs = linaclotide," but unless we see evidence that the market is moving toward this view (and away from the tag of chronic constipation), we will remain hesitant to buy-into this drug's blockbuster CC potential. A key component of commercial success or failure in this area will be decision by payers on whether to reimburse for this indications. *Where we could be wrong: We are straddling a middle ground. The drug could prove less successful than we now estimate, especially if safety problems emerge or reimbursement is too difficult. Alternatively, if the company and its partners can change the way physicians think about this market, chronic constipation could grow into a market at least as large as IBS-C. Though there are a number of over-the-counter drugs available for chronic constipation, these drugs do not significantly help with abdominal discomfort and bloating, and there are a meaningful number of patients that are not satisfied with current therapies (~45%).*
How and when will the company build a deeper pipeline to support its significant top-line potential?	Company could fail to invest future cash flows wisely or build a pipeline beyond linaclotide. Long-term growth beyond linaclotide is uncertain and risk remains concentrated.	We do not differ considerably from consensus except that we are more comfortable than consensus that management will protect shareholders' long-term interests. Our discussions with management suggest that they will be careful capital allocators, focused on internal development candidates and early-stage assets, where risk-adjusted ROI is the highest (but slowest). Given the significant cash flows this company has the potential to generate and its hesitancy about big acquisitions, we would not be surprised if it became a payer of dividends relatively early in its life-cycle. It is worth noting, though, that management and several shareholders control the vote on any change of control. Therefore, if management spends cash unwisely, an acquirer may not be able to extract value unless management consents.

Risk-Reward Snapshot: Ironwood Pharmaceuticals (IRWD, OW, PT $19)

Linaclotide benefit on abdominal pain and penetration in chronic constipation drives risk/reward:



Source: Company data, Morgan Stanley Research

Bull Case $28	**DCF based intrinsic value**	**Linaclotide gains greater acceptance in chronic constipation than expected with total sales >$2bn.** Our bull case assumes greater sales in chronic constipation, as the drug's effects on abdominal discomfort, bloating etc. are enough to drive use in this market (our market penetration estimate grows to ~30% of the addressable patient population - still <10% of patients currently diagnosed and seeking treatment). This scenario will take longer to play out than either of our other scenarios (need to see commercial trends), and over the next year, investors will largely be dealing with whether the base or bear case plays out.
Base Case $19	**DCF based intrinsic value**	**Linaclotide improves abdominal pain and sells ~$1bn in IBS-C, but struggles to gain meaningful penetration in chronic constipation.** Our base case assumes linaclotide shows a large enough benefit on abdominal pain (data 2H10) to drive meaningful use in IBS-C, but chronic constipation remains a challenging market commercially given the number of over-the-counter options. We estimate Ironwood's share of those patients diagnosed with IBS-C and currently unsatisfied with therapy of ~40-45%. **The key to this scenario will be the Phase III data in 2H2010.**
Bear Case $8	**DCF based intrinsic value**	**Linaclotide fails to show improvement on abdominal pain and drug falters commercially in IBS-C.** Abdominal pain is the key potential point of differentiation for this drug. Failure to show this benefit in upcoming Phase III trials in 2H10 would significantly limit its commercial success as IBS-C patients are largely defined by their abdominal pain. In this scenario, we assume penetration of the addressable patient population (IBS-C patients that are diagnosed and not satisfied with current therapies) of ~15-20% (equates to <2% of individuals with IBS-C symptoms). Our chronic constipation assumptions are similar to our base case.

Investment Thesis

- We believe investors underestimate the probability that linaclotide. Ironwood's late stage drug for irritable bowel syndrome with constipation (IBS-C) and chronic constipation (CC), will show a significant improvement on abdominal pain in Phase III IBS-C trials. We expect this benefit to be a key point of commercial differentiation and the main 2010 stock catalyst.

- We have peak estimates for WW sales of linaclotide of >$1 bn, which is above investor expectations.

- Ironwood retains significant ownership in linaclotide (has partnered in most of world), and the company gains significant operating leverage if the drug reaches our peak estimates. We estimate peak EPS of >$2.50.

Risks

- Linaclotide could fail in Phase III trials for IBS-C
- Linaclotide could struggle to gain meaningful traction commercially
- Ironwood could fail to both invest future cash flows wisely and build a pipeline beyond linaclotide
- The company still needs to complete linaclotide carcinogenicity studies, and while preliminary results are benign, final data are due in 2H10

Potential Catalysts

- **May 2010:** Presentation of Phase III chronic constipation data at Digestive Disease Week
- **2H10:** Data from two Phase III IBS-C trials
- **1H11:** Submission of NDA
- **Early 2012**: Potential US launch
- **2013:** Potential EU launch

Investment Case

Summary & Conclusions

We are initiating coverage of Ironwood Pharmaceuticals with an Overweight rating and price target of $19
Ironwood has one drug candidate, linaclotide, in late stage development for the treatment of chronic constipation (CC) and irritable bowel syndrome with constipation (IBS-C). Linaclotide is a guanylate cyclase type C agonist, and the company has already reported positive Phase III results from two trials in CC. Data from two additional Phase III trials in IBS-C will be available in the fall of 2010, and we expect the outcome of these data will be the key determinant in 2010 stock performance. We are optimistic about these data and believe results will move the stock toward our $19 price target.

The key debates for IRWD are: 1) will linaclotide show a benefit on abdominal pain in its Phase III trials; 2) what is the potential commercial opportunity of linaclotide in both IBS-C and chronic constipation; and 3) how will the company allocate capital and build a pipeline beyond linaclotide. We believe investors overestimate the risk to Phase III trials in IBS-C and underestimate the commercial opportunity in this indication.

Phase II and III data to date are strong and portend success in upcoming Phase III trials
IBS-C is a widespread disease affecting mostly women and characterized by constipation ***and*** abdominal pain. No drug to date has demonstrated a meaningful impact on abdominal pain, and success for linaclotide on this endpoint could provide a critical point of differentiation and enable greater commercial success. While many investors are skeptical on this endpoint, especially given the fickleness of pain as an endpoint, data to date suggest a high probability of success, in our view.

The Phase III IBS-C patient population is similar to Phase IIb, with the key difference between trials being modification of the primary endpoint—in Phase IIb the endpoint was change in complete spontaneous bowel movement (CSBM) frequency, while the Phase III primary endpoint includes CSMB ***and*** improvement in abdominal pain. In the Phase IIb trial in IBS-C, 300 mcg of linaclotide (Phase III dose) led to a 170% increase in reaching the Phase III primary endpoint (27% vs. 10%). The trial also showed a significant benefit in pain with responder rates of 48% vs. 30%. Phase IIb data in IBS-C and Phase III data (as well as Phase IIb data) in CC have consistently shown that this drug meets all its primary **and** secondary endpoints, as the drug effect in these diseases is clear. Our physician diligence is also quite positive on the probability of success.

Targeting large potential markets and even modest penetrations lead to blockbuster sales
Current estimates in the US suggest 11mn people suffer from IBS-C and 30 mn people suffer from CC. We and our consultants believe that IBS-C offers the more compelling commercial opportunity, as the patient suffering is greater and the treatment alternatives offer meaningfully less relief (fiber and laxatives as well as off-label use of anti-depressants often exacerbate bloating and abdominal pain).

We estimate that only ~30% of IBS-C patients are satisfied with current treatments and that linaclotide, should it show improvements in abdominal pain, has a clear window of opportunity in those patients not satisfied with current therapies. Additionally, its better side effect profile may allow it to capture some share among those satisfied with current therapies (although this is not part of our model). Our ~$850 mn US peak sales estimate in IBS-C assumes penetration in <5% of the overall IBS-C population and 40-45% of those patients seeking treatment and not satisfied with current drugs.

Though chronic constipation (CC) has more patients, we expect sales in this market to be lower than in IBS-C, as pain and abdominal discomfort are less severe. There are also a number of relatively effective over-the-counter options, so reimbursement and physician acceptance will likely be more challenging. We assume penetration in CC will be limited and that US peak sales will be $400-500mn (<1% of overall CC population and <10% of those seeking care and not satisfied).

Solid partnerships with significant economics in place
Ironwood has partnerships in place in the US (**Forest**; 50/50 profit split), EU (**Almirall**; royalty where Ironwood has stated the terms approach ~50% of the profits assuming modest sales) and most of Asia (**Astellas**; we estimate royalty of high-teens/low 20s).

In the US, Ironwood has a 50/50 profit split with Forest (Ironwood will provide 35% of primary care sales reps). We are confident in Forest's ability as a partner as it has primary care commercial experience in competitive markets and is motivated to sell the drug given its pending patent cliff. As with any primary care drug, there will be significant upfront investments (we estimate drug turns profitable with ~$400 mn in sales), but any sales beyond that have extremely high incremental margins. We believe peak earnings for this company will exceed $2.50/share, which suggests even a

modest multiple expansion can lead to meaningful upside over the next several years.

Key upcoming catalysts include: 1) presentation of Phase III chronic constipation data at Digestive Disease Week in May; 2) data from two Phase III trials in IBS-C (2H10); 3) submission of linaclotide NDA (1H11); 4) potential FDA approval of linaclotide for IBS-C and CC (2012).

Solid IP Estate

Linaclotide has a solid IP estate in place that should allow for substantial cash flow generation over the 15 years. The drug is protected by a US composition of matter patent that expires in 2025, an EU composition of matter patent that expires in 2024, and a pending patent application in Japan, that, if issued, would expire in 2024 as well. In addition, the company has filed formulation patents for orally delivered peptides that, if issued, could extend well beyond 2025 (but we consider composition of matter the stronger protection). We estimate that from drug launch through 2020, linaclotide will generate over $1bn in free cash flow.

There are several risks to our thesis:

1) Linaclotide could fail in Phase III trials for IBS-C in a number of ways: a) it could miss the primary endpoint, which would likely lead to a decision to run another trial, increasing R&D expectations and delaying time to the market; b) it could fail to show a convincing improvement in abdominal pain, which we do not believe would prevent approval in IBS-C given the other drugs on the market, but may limit sales; or c) an unexpected safety issue could occur.

2) Linaclotide could fail to gain meaningful commercial traction. Though linaclotide is targeting large markets, and, in our opinion, has significant commercial potential, the track record for prescription medicines in the IBS-C and CC markets are mixed, at best. The modest efficacy and side effects of other prescription agents (e.g. Amitiza) and Zelnorm's previous withdrawal from the market may lead to hesitancy amongst physicians to adopt a new drug in this area. In addition, there are competitors several years behind in development.

3) Ironwood could fail to invest future cash flows wisely and build a pipeline beyond linaclotide. All pipeline candidates beyond linaclotide are in Phase I and long-term growth will depend on the company's ability to reinvest its cash flows in a way that either drives growth organically or via strategic actions (or return the cash to shareholders).

Valuation. Overweight. Price Target $19.

Our $19 price target is based on a discounted cash flow (DCF) analysis that uses a WACC of 12.5%, an intermediate growth rate of 8% and a terminal growth rate of 2.5%. This estimate is ~25X 2015 fully-taxed and fully-diluted EPS of $1.27 discounted back to 1Q11 (one year from now) at a rate of 15%. The implied multiple is 18X our actual expected EPS, as the company will not pay taxes for several years given its net operating losses (NOLs). While the primary methodology for our price target is DCF, we believe the discounted earnings methodology provides a sanity check. A 15% discount rate, in our opinion, is consistent with what the market typically demands for drugs with positive Phase III data and a 20-30x multiple (on actual and fully-taxed EPS, respectively) is in line or moderately conservative compared to the multiple awarded to current small-molecule based companies.

Exhibit 1

DCF analysis supports $19 price target

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Free Cash Flow (w/o option expense)	3,897	-107,643	-85,902	-99,607	-162,542	-44,081	227,587	232,786	259,014	279,735	302,113
		-2862.09%	*-20.20%*	*15.95%*	*63.18%*	*-72.88%*	*-616.30%*	*2.28%*	*11.27%*	*8.00%*	*8.00%*
Free Cash Flow (w/ option expense)	3,897	(107,643)	(85,902)	(99,607)	(162,542)	(44,081)	227,587	232,786	259,014	279,735	302,113
Y		*-2862.09%*	*-20.20%*	*15.95%*	*63.18%*	*72.88%*	*-616.30%*	*2.28%*	*11.27%*	*8.00%*	*8.00%*
Present Value of Free Cash Flow			-78,640	-81,054	-117,570	-28,342	130,068	118,258	116,962	112,283	107,792

Discounted Cash Flow (DCF) Business Valuation ($ millions)	
WACC Applied (%)	12.5%
Intermediate Growth rate	**8.0%**
Terminal Growth Rate (%)	**2.5%**
Discounted Net Cash Flow	**279,758**
Terminal Value	3,096,662
Discounted Value of Terminal Value	**1,242,973**
Terminal Value as % of total	81.6%
Firm Value	**1,522,731**
Net Debt	(244,465)
Equity Value	**1,767,196**
Shares Outstanding (thousand)	94,396
Equity Value per Share ($)	**$19**

Source: Company data, Morgan Stanley Research

Debate 1: Will Phase III Data in IBS-C Show a Benefit in Treating Pain?

Irritable bowel syndrome with constipation (IBS-C) is a disease characterized by a combination of constipation and abdominal pain. Data suggest that the disease affects ~11 mn people in the US (with a similar number in the EU), primarily women between 25-40. Currently approved drugs (as well as Novartis' Zelnorm, which was removed from the market) have been able to show a benefit in relieving constipation, but they have not been able to show a benefit on pain. This lack of benefit on pain and discomfort has decreased acceptance, lowered compliance when prescribed (patients do not take pills every day), and led to high discontinuation rates in the marketplace.

Ironwood, and its partners, will release data from two Phase III trials in IBS-C in 2H10. These trials contain a three-pronged primary endpoint that looks at: 1) complete spontaneous bowel movement (CSBM) responders; 2) abdominal pain responders; and 3) patients that meet both endpoints. Based upon the approvals of other drugs, we believe the drug is approvable with an indication in IBS-C as long as it hits the CSBM responder endpoint. However, it will need to hit all three endpoints to get an indication for the treatment of abdominal pain, which will be an important differentiator in the market.

We spoke to a number of investors during the roadshow, and both bulls and bears were confident that linaclotide will meet its CSBM endpoint (we agree). However, there is significant uncertainty around the probability that the drug will show a benefit on abdominal pain in the Phase III trials for IBS-C. Our bear case assumes that the drug does not show a benefit in abdominal pain, in which case even with success on the CSBM primary endpoint, the stock may see downside ($8/share) before seeing upside over time.

While IBS-C has typically been hard to treat and no drug has had a meaningful mitigating effect on pain, we remain confident that linaclotide has a high chance of success of meeting this endpoint.

We and Street expect linaclotide to show an increase in bowel movements

Ironwood is currently running two Phase III trials in IBS-C, each of which consists of ~800 patients.

Study 302 is a 26-week, 800 patient trial looking at 300 mcg linaclotide vs. placebo

Study 31 contains a 12 week drug period (300mcg dose) with a 4 week randomized withdrawal in ~800 patients.

In the Phase III trials the primary endpoint consists of three efficacy parameters: 1) 12 week abdominal pain and CSBM responder; 2) 12 week CSBM responder; and 3) 12 week abdominal pain responder (see Exhibit 2 for details).

Exhibit 2

IBS-C Phase III Primary Endpoints

Endpoint	Definition
CSBM Resonder	9/12 weeks has ≥3 complete spontaneous bowel movements and ≥1 increase from pre-treatment baseline
Abdominal Pain Responder	9/12 weeks has ≥30% relative reduction in abdominal pain vs. baseline
CSBM and Abdominal Pain Responder	Meets both of the above defined criteria

Source: Company data, Morgan Stanley Research

Based on strong data to date, we are confident that linaclotide will hit its CSBM responder endpoint.

Exhibit 3

Linaclotide showed significant benefits on the Phase III endpoints in the Phase IIb trial

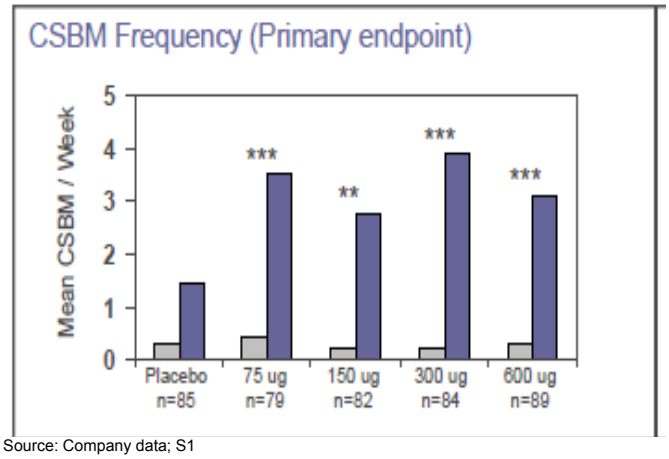
	300mcg linaclotide	Placebo
CSBM Responder	31%	13%
Pain Responder	48%	30%
CSBM and Pain Responder	27%	10%

Source: Company data, Morgan Stanley Research

Phase II data in IBS-C. Ironwood has conducted a 420 patient Phase IIb study in IBS-C at 92 sites in the US and Canada. The study had a two-week pretreatment baseline period, a 12-week treatment period, and a two-week post treatment period. This study evaluated change in weekly CSBM frequency as well as additional endpoints including SBMs, stool consistency, straining, abdominal pain, discomfort, bloating etc. During the baseline period, the average CSBM frequency was 0.3 CSBMs per week and 68% of patients had no CSBMs during this period. The change from baseline in weekly CSBM frequency vs. placebo was statistically significant ($p<0.01$) in all lincalotide dosing arms compared to the placebo group. This drug clearly helps patients have bowel movements.

Exhibit 4

In its Phase IIb IBS-C trial, linaclotide met its weekly CSBM frequency endpoint with statistical significance at all doses



Source: Company data; S1

A similarly strong effect on bowel movements was observed in the Phase III chronic constipation trial. Ironwood has released data from its two Phase III trials in chronic constipation. These trials included >600 patients each and tested linaclotide's effect on 12-week CSBM responder rates (12-week CSBM responder is a patient who had three or more CSBMs per week and an increase of at least one CSBM per week over baseline for at least nine of the 12 weeks; the same CSBM endpoint as in the IBS-C Phase III trials (see Exhibit 2)). During the baseline period, average CSBM frequency in these trials was 0.3CSBMs per week and 68%-72% of patients had no CSBMs during this period. Both trials met the primary endpoint with statistical significance (Exhibit 5) and led to >3 fold numerical increases in CSBM responders.

Exhibit 5

Linaclotide's effect on bowel movements in Phase III chronic constipation were strong

	Linaclotide		
	133 mcg	266 mcg	Placebo
LIN MD 01 Trial	N = 213	N = 202	N = 215
Primary Endpoint			
12-Week CSBM Overall Responder	34 (16.0%) p = 0.0012	43 (21.3%) p < 0.0001	13 (6.0%)
Secondary Endpoints			
Overall CSBM Rate Change ≥ 1	105 (49.3%) p < 0.0001	115 (56.9%) p < 0.0001)	55 (25.6%)

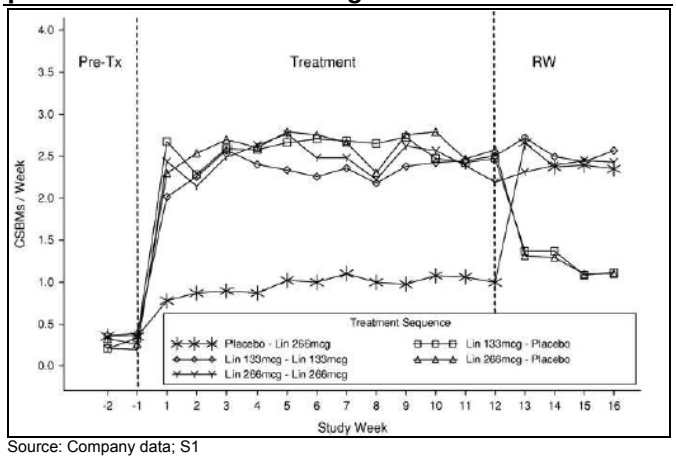
Endpoint	Placebo (N = 209)	133 mcg (N = 217)	266 mcg (N = 214)
Primary Endpoint			
12-week CSBM responder (1)	3.3%	21.2% (p<0.0001)	19.4% (p<0.0001)
Additional Endpoints			
CSBM rate change ≥ 1 responder (2)	11.0%	39.2% (p<0.0001)	37.0% (p<0.0001)
CSBM rate ≥ 3 responder (3)	3.8%	21.7% (p<0.0001)	19.4% (p<0.0001)
12-week CSBM mean change ≥ 1 responder (4)	22.5%	55.8% (p<0.0001)	52.8% (p<0.0001)

Source: Company data; S1

Further support for the drug's efficacy is provided by the four-week randomized withdrawal period following the 12-week treatment period in which linaclotide treated patients re-randomized to placebo exhibited bowel and abdominal symptoms similar to those seen in the placebo group during the treatment period (see Exhibit 6), and by the fact that in five of the six Phase II and III trials, diarrhea was the most common adverse event (seen in 5-20% of subjects).

Exhibit 6

Mean weekly CSBMs decreased rapidly after patients were taken off drug



Source: Company data; S1

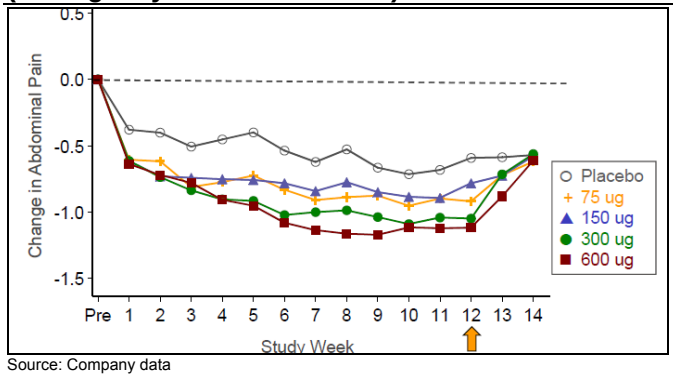
The key question is whether linaclotide will hit its abdominal pain endpoint.

Though an improvement in CSBM is important and crucial to

the regulatory approval of this drug, blockbuster commercial potential largely depends on lincalotide showing a benefit on abdominal pain, as it would be a key differentiating feature.

We believe Phase IIb results point to Phase III success
Phase IIb was successful with an improvement in constipation symptoms throughout week 12 (discussed above) and rapid reductions in abdominal pain, discomfort and bloating. Abdominal pain was reduced 37-47% and pain reduction was observed within the first week following initiation of therapy.

Exhibit 7
Linaclotide led to significant reductions in abdominal pain scores in Phase IIb data in IBS-C (dosing only for first 12 weeks)



Source: Company data

The Phase III patient population is quite similar to Phase IIb. There are two principal differences between the two trials: the primary endpoint (which we discussed above) and the pain scale.

Pain scale: In the Phase IIb trial, pain was measured using a five-point ordinal severity scale, with "1" being no pain and "5" being very severe. In the Phase III trial, the pain scale being used is an 11-point scale (0=none to 10= very severe). This change was made, according to the company, in order to please the pain division at the FDA, which prefers the 11-point scale. Despite these changes in trial design, we believe Phase IIb results predict Phase III success.

Changing measuring scales in Phase III trials can increase risk to the trial, but we are confident that linaclotide will show a reduction in pain that is both significant and large enough to offset any concerns over clinical relevance as:

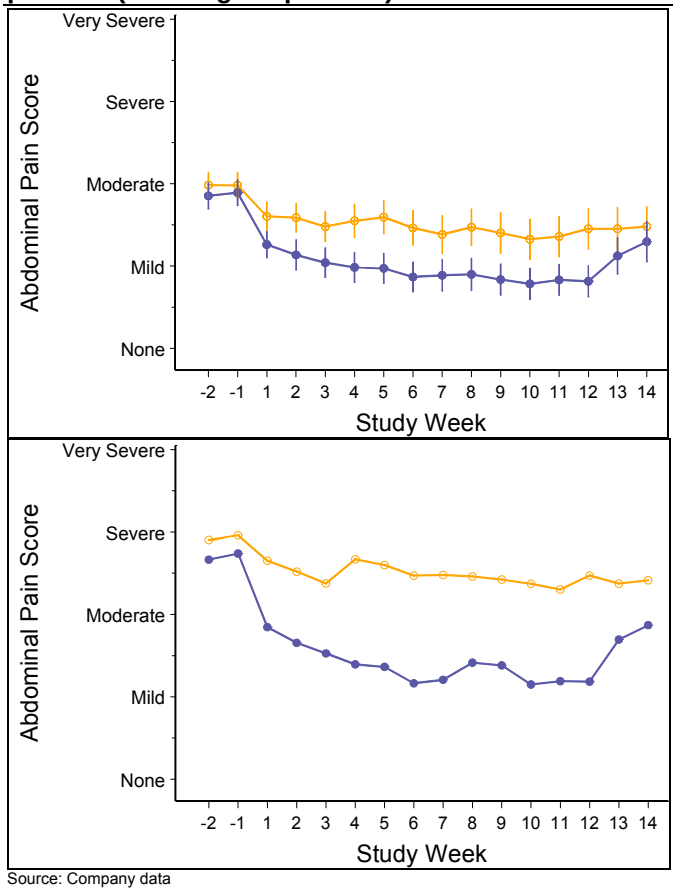
1) *The eleven-point scale has been found to be more sensitive than the five point scale.* Both a four-point pain scale and 11-point pain scale have been used in migraine studies to assess treatment efficacy. Data have shown that 11-point pain scale scores are highly correlated with four-point pain scores in migraine headaches, and that the 11-point pain scale is meaningfully more sensitive than the four-point pain scale in detecting clinically important differences (WJ Kwong et al. *Validation of the eleven-point pain scale in the measurement of migraine headache pain*, Cephalagia 2007). Though a different pain, this result is interesting and adds support to the validity and sensitivity of the eleven-point pain scale.

2) *It may take more for an individual to believe they have improved two points on a scale instead of one.* Patients need to show a 30% improvement in pain in 9 of 12 weeks to meet the primary endpoint. Given that the average pain score at baseline is in the 5-6 range, patients will need to have improvements of ~2 points on the pain score in order to meet the criteria. In Phase II, patients only needed to move from a baseline of 3 to a new score of 2. We believe it may take more for a patient to move 2 points on a larger scale than 1 point on a smaller scale. Generally, pain trials benefit from decreasing placebo response rates, which should mean the trial has a greater probability of success. Therefore, while this change in protocol may decrease overall response rates, it may actually improve the probability of success (although we generally view any changes in Phase III protocol as introducing some element of risk).

3) *The patient population in Phase III is sicker than in Phase IIb and to date, the drug has shown a larger benefit in more severe patients*. The baseline values in the Phase IIb trial ranged from 2.87 to 3.13 (2 is categorized as mild and 3 moderate). In Phase III, patients needed to have an abdominal pain score of at least 3 at baseline and, as we understand, the average baseline score in the trial ended up being around 6.5 ("severe"). The inclusion of more severe patients gives us added comfort on the pain endpoint, as Phase IIb data suggest that severe patients show a greater benefit from linaclotide (see Exhibit 8).

Exhibit 8

Linaclotide reduced abdominal pain in moderate patients, but benefit was more pronounced in severe patients (300 mcg vs. placebo)



Source: Company data

Phase III chronic constipation data also bode well for abdominal pain improvement in Phase III IBS-C trial.

In its Phase III CC trial, linaclotide met all secondary endpoints including bloating, abdominal discomfort, stool consistency, straining, and constipation severity with P<.001. These results were very consistent with Phase IIb. While abdominal pain was *not* an endpoint in this trial (chronic constipation patients by definition have little "pain"), the results on abdominal discomfort and bloating were quite encouraging (Exhibit 9). We see only a fine line between "pain" and "discomfort" and believe success in one portends success in the other. Importantly, bloating and discomfort correlated with pain in the Phase IIb IBS-C trial and more data showing improvement on this endpoint bode well for potential pain improvements in the Phase III IBS-C trial.

Exhibit 9

Linaclotide showed benefits on abdominal discomfort and bloating in Phase III CC

	Placebo	266mcg (aka 300mcg)
Trial 1		
Abdominal discomfort	19.5%	33.5%
Bloating	13.0%	27.3%
Trial 2		
Abdominal discomfort	21.1%	30.3%
Bloating	13.2%	22.0%

Source: Company data

Exhibit 10

In Phase IIb IBS-C, abdominal pain improvements correlated with benefits on abdominal discomfort and bloating

	Placebo	300mcg
Abdominal pain	25.6%	46.8%
Abdominal discomfort	22.1%	42.7%
Bloating	16.1%	37.3%

Source: Company data

Mechanism of action suggests success.

Linaclotide's mechanism of action provides scientific rational as to why this drug has a meaningful effect on both bowel function and pain. Linaclotide is a stable peptide analog of guanylin/uroguanylin and binds to guanylate cyclase type-C (GC-C) receptors found on epithelial cells that line the intestine. When linaclotide binds, these receptors become activated. Activation of GC-C receptors leads to increases in both intracellular and extracellular cGMP. It is believed the increased cGMP: 1) excites the epithelial cells to block pain signaling by inhibiting pain sensing neurons that carry signals from the GI tract to the central nervous system; and 2) remains inside the epithelial cell where it actives anion channels, which leads to increased fluid secretion into the intestinal lumen (thus aiding bowel movement).

Debate 2: What Penetration Is Reasonable in IBS-C?

IBS-C is the larger market opportunity for linaclotide, in our opinion, as patient urgency is greater (patients sicker and more uncomfortable than those with chronic constipation) and there are fewer effective therapies. A key debate in the market is how big will linaclotide be in this indication, as it will likely be the main driver of sales. We believe, if linaclotide is able to improve abdominal pain, the drug has blockbuster sales potential in this indication.

Street concerns largely center around the fact that: 1) launches into new primary care categories are often slow and difficult to predict; IBS-C is a widespread illness, but there is limited evidence that it is a large commercial market to date; 3) the most recently approved drug for this indication, Takeda's Amitiza, had faltered commercially (~$200mn annually almost four years post launch); 4 following withdrawal of Novartis' Zelnorm from the market, physicians may be hesitant to adopt novel agents in this disease area; 5) patients can try over-the-counter alternatives that are cheap and preferred by third-party payers; and 6) in Europe, Ionwood's partner Almirall does not yet have pan-European infrastructure.

We believe linaclotide has a profile that separates it from past drugs in this market and anticipate >$1bn in peak sales in IBS-C (abdominal pain improvement is assumed in our base case estimates).

Room for market growth

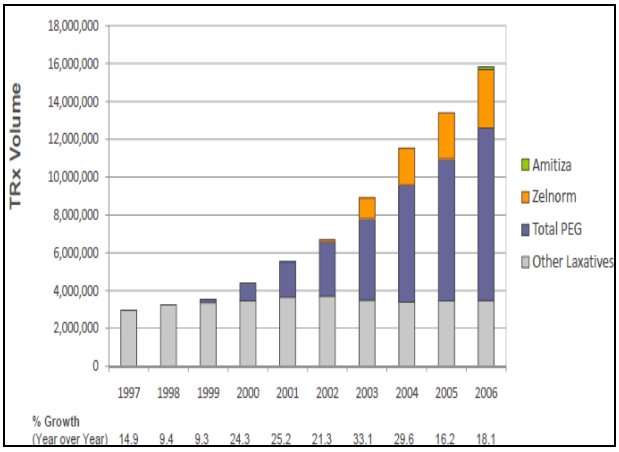
Irritable bowel syndrome with constipation IBS-C affects ~11mn individuals in the US (predominately women between 25-40). The disease is characterized by constipation, pain, bloating, and discomfort. The number of approved prescription therapies for IBS-C has been limited to date and consensus among physicians is that current over the counter and branded therapies offer little relief. Physician diligence offers little doubt that linaclotide's data to date suggest it will be a differentiated drug in this market.

Novartis' Zelnorm was the first drug approved (2002) for short-term treatment of women with irritable bowel syndrome whose primary bowel syndrome is constipation. Zelnorm was pulled from the market in 2007 after an FDA analysis of safety data pooled from 29 clinical trials involving over 18,000 patients showed an excess number of serious cardiovascular events in patients taking Zelnorm (0.11%) compared to patients given placebo (0.1%). It is worth noting that these data suggest there will be limited tolerance amongst regulators if there is any hint of a serious side effect during the reminder of clinical trials.

Zelnorm's approval led to a greater than doubling in prescription volumes between 2002 and 2006 (see Exhibit 11), and it was on an ~$600 mn run rate prior to its withdrawal despite only modest efficacy on either bowel movements or pain/discomfort (see Exhibits 12 & 13) and concerns about its cardiovascular safety. Following Zelnorm's withdrawal, the IBS-C market shrunk (Exhibit 14), indicating clear room for a novel effective to both grow and take substantial share of the market.

Exhibit 11

IBS-C market grew significantly following Zelnorm launch



Source: Ironwood slides, IMS, NGPS, NPA

Exhibit 12

Zelnorm was on a $600mn+ runrate prior to withdrawal despite only modest efficacy on bowel movements

	Zelnorm 6mg BID (n=440)		Placebo (n=431)		
	Baseline	Weeks 1-12	Baseline	Weeks 1-12	Placebo Adjusted Difference
Number of SBM/week	3.5	5.4	3.7	4.6	
Change in SBM		**1.9**		**0.9**	**1.00**
Number of CSBM/week	0.6	1.9	0.6	1.3	
Change in CSBM		**1.3**		**0.7**	**0.60**
	Amitiza 24mcg BID		**Placebo**		
	Baseline	Week 4	Baseline	Week 4	Placebo Adjusted Difference
Number of SPM/week	1.4	5.3	1.6	2.9	
Change in SBM		**3.9**		**1.3**	**2.60**
Number of CSBM/week	NA	NA	NA	NA	
	Linaclotide 300mcg		**Placebo**		
	Baseline	Weeks 1-4	Baseline	Weeks 1-4	Placebo Adjusted Difference
Number of SBM/week	2.2	5.8	2.3	3.8	
Change in SBM		**3.6**		**1.5**	**2.10**
Number of CSBM/week	0.5	2.3	0.5	1	
Change in CSBM		**1.8**		**0.5**	**1.30**
	Baseline	Weeks 1-12	Baseline	Weeks 1-12	Placebo Adjusted Difference
Number of SBM/week	~2	5.7	~2	3.1	
Change in SBM		**3.7**		**1.1**	**2.60**
Number of CSBM/week	0.3	3	0.3	0.9	
Change in CSBM		**2.7**		**0.6**	**2.10**

Source: Product labels, Johanson et al. Effect of Tegaserod in Chronic Constipation: A Randomized Double-Blind, Controlled Trial, Clinical Gastroenterology and Hepatology, 2004; Lembo et al. Efficacy of Linaclotide for Patients with Chronic Constipation, Gastroenterology, 2010; Ironwood data

Exhibit 13

Linaclotide has shown much greater effects on abdominal symptoms than Zelnorm

Symptom	Zelnorm relative to placebo
Abdominal pain/discomfort	1-10%
Bloating	4-11%
Symptom	**Linaclotide relative to placebo**
Abdominal pain	21.2%
Abdominal discomfort	20.6%
Bloating	21.2%

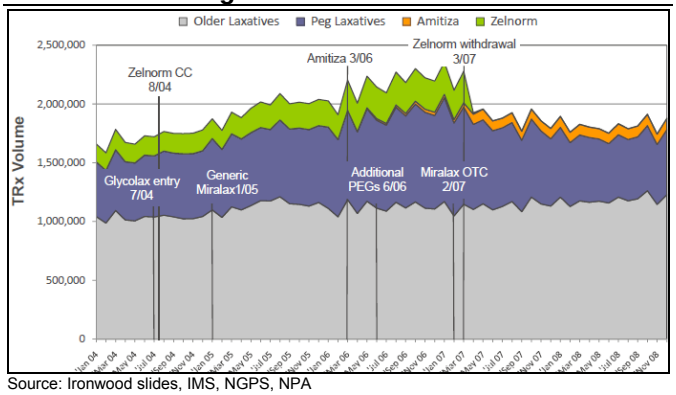
Source: Zelnorm label; linaclotide IBS-C Phase IIb data

Linaclotide's profile is convincing even to a conservative physician base

IBS-C is largely a primary care market, and drugs targeting gastrointestinal (GI) diseases have had an abnormally high number of safety issues over the past decade (beyond Zelnorm, Resolor, Propulsid, and Lotronex have either been withdrawn from the market or faced significant restrictions). While GI diseases often cause meaningful patient distress, they rarely are fatal, which decreases physician urgency.

Exhibit 14

Trends following Zelnorm withdrawal show clear room for market growth



Source: Ironwood slides, IMS, NGPS, NPA

Linaclotide has the best efficacy and safety in IBS-C to date. Linaclotide has met its primary endpoint of increased complete spontaneous bowel movement frequency in every trial conducted to date and continues to show benefits on secondary endpoints including pain, bloating, discomfort etc. Neither Zelnorm nor Amitiza had meaningful beneficial effects on abdominal symptoms. Additionally, Amitiza sales have been disappointing largely due to high rates of nausea

associated with the drug.

Linaclotide safety has been quite clean to date with the only notable side effect being modest increases in diarrhea (consistent with the drug's mechanism). In addition, linaclotide is not absorbed and has no effect on the serotonin system (Zelnorm and many others withdrawn from market all worked through serotonin receptors in the gut). The lack of systemic absorption and novel mechanism decreases the risk of side effects or significant toxicity.

Exhibit 15

Linaclotide safety has been clean in both IBS-C and CC to date

IBS-C Phase IIb

	Placebo (n=85)	300mcg Linaclotide (n=85)
Any treatment emergent adverse event	41%	59%
Diarrhea	1%	16%
Abdominal pain	4%	5%
Urinary tract infection	2%	6%
Nausea	6%	1%
Nasopharyngitis	6%	1%
Upper respiratory tract infection	4%	5%
Sinusitis	2%	4%
Bronchitis	0	1%
Back pain	1%	1%
Fecal incontinence	0	0

Chronic Constipation Phase III

	Trial 303		Trial 01	
	Placebo	Linactlotide	Placebo	Linactlotide
N	209	434	215	418
Any treatment emergent adverse event	50%	56%	54%	61%
Diarrhea	7%	13%	3%	17%
Flatulence	4%	4%	6%	7%
Upper respiratory tract infection	NA	NA	7%	6%
Abdominal pain	4%	3%	2%	5%
Nausea	4%	4%	3%	4%
Abdominal distension	1%	3%	3%	4%
Urinary tract infection	NA	NA	4%	3%
Sinusitis	1%	3%	2%	3%
Nasopharyngitis	3%	3%	3%	3%
Headache	4%	4%		
Abdominal pain upper	1%	2%		

Source: Company data, Morgan Stanley Research

We believe linaclotide's profile to date is convincing and given the unmet need in the IBS-C market and patient urgency (some patients have meaningful pain), we and our physician consultants expect this drug to gain significant traction in this market. We estimate ~12% of the IBS-C population is currently diagnosed and treated, but only 30% of the population is satisfied with current therapies. We assume linaclotide peak penetration of <5% of the overall IBS-C population, and 40-45% of patients seeking care and unsatisfied with current therapies (see Exhibit 16).

Forest is strong US marketing partner; Almirall carries more risk

Linaclotide has partnered with Forest (FRX, Overweight, covered by David Risinger) in the US. Forest has primary care commercial experience in competitive markets and is motivated to sell the drug given its pending patent cliff. Forest has competed effectively in a number of markets, including depression (Lexapro and Celexa), hypertension (Bystolic), and Alzheimer's disease (Namenda). We expect the companies (Forest and Ironwood) to staff ~1,000 sales representatives, of which Ironwood has the right to hire 35%.

One important nuance that needs to be addressed still is that Forest has historically been reticent to participate in direct to consumer advertising, and as far as we know, has never advertised on television. Zelnorm sales were very sensitive to marketing effort, and maximum sales potential will likely require Forest to agree to more aggressive marketing.

While economics in Europe are favorable (royalty structure, but Ironwood could share ~50% of long-term value if certain sales level are met, which we understand are relatively modest), Almirall has more risk. Almirall is a leading marketing company in Spain, and it plans to use linaclotide to build its pan-EU presence. While this creates dynamics of a motivated partner, it leaves open the possibility that Almirall will either: 1) not be willing to spend to optimize the brand given P&L constraints or 2) has execution issues.

Competitors 3+ years behind in development

A few companies are developing products which would compete with linaclotide should they be FDA approved, though we see no competitive threats near-term.

Synergy Pharmaceuticals has a drug (**SP-304**) similar to linaclotide that targets GC-C receptors in the GI tract. This drug is also being developed in IBS-C and chronic constipation. SP-304 has completed its initial Phase I safety trial in volunteers and recently began a Phase IIa clinical trial in chronic constipation. This trial will enroll ~60 patients and will evaluate the safety of the drug as well as its effect on bowel habits over a 14 day period. Data from this study will be available later this year. Though SP-304 may have potential, we have seen little data to date (and it is unlikely a 14 day study will provide much information as these drugs are chronic and longer-term safety and efficacy is necessary).

This company's founders worked with several of the scientists at Ironwood in previous careers, and while we have limited information on the drug, our diligence has been generally optimistic. It is 3-5 years behind and will need significant human and toxicology data. Second-to-market drugs have increasingly had difficulty displacing market leaders without a differentiated profile. Regardless, investors should keep an eye on this drug.

US IBS-C is largest opportunity in our view, but EU could provide upside

Our EU sales estimates are ~35% of US peak sales owing to lower pricing, a more difficult reimbursement environment, and less certainty about the partner. If the drug shows a benefit in pain, our price and penetration rates may prove too conservative and may be the lowest bar for upside to our estimates.

Exhibit 16

We estimate peak WW sales in IBS-C of >$1bn

US Irritable Bowel Syndrome-constipation	2008	2009	2010E	2011E	2012E	2013E	2014E	2015E	2016E	2017E
US Population	304,059	307,100	311,706	316,382	321,127	325,944	330,833	335,796	340,833	345,945
% with IBS-C symptoms	*4%*	*4%*	*4%*	*4%*	*4%*	*4%*	*4%*	*4%*	*4%*	*4%*
People with IBS-C symptoms	11402	11516	11689	11864	12042	12223	12406	12592	12781	12973
% Diagnosed and treated with Rx	12%	12%	12%	12%	13%	13%	14%	14%	15%	15%
Patients treated for IBS-C with Rx	1368	1382	1403	1424	1517	1577	1712	1813	1917	1946
% on treatment and satisfied	30%	30%	30%	30%	30%	31%	31%	32%	33%	34%
Linaclotide eligible patients	958	967	982	997	1062	1096	1181	1233	1285	1294
Linaclotide penetration	0%	0%	0%	0%	9%	16%	26%	34%	40%	43%
Patients on Linaclotide	0	0	0	0	96	175	307	419	514	556
Cost per month	$0	$0	$0	$210	$214	$218	$223	$227	$232	$236
Duration of therapy	0	0	0	0	4	5.5	6	6.5	6.5	6.5
Revenue per patient	$0	$0	$0	$0	$857	$1,202	$1,337	$1,478	$1,507	$1,537
Total US IBS-C Sales	$0	$0	$0	$0	$81,903	$210,694	$410,689	$619,427	$774,341	$855,370
EU Irritable Bowel Syndrome-constipation	**2008**	**2009**	**2010E**	**2011E**	**2012E**	**2013E**	**2014E**	**2015E**	**2016E**	**2017E**
EU population	491018	491509	492001	492493	492985	493478	493971	494465	494960	495455
% with IBS symptoms	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
% with IBS-C	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*	*33%*
Number with IBS-C symptoms	15393	15409	15424	15440	15455	15471	15486	15501	15517	15533
% Diagnosed and treated	*5%*	*5%*	*5%*	*5%*	*5%*	*6%*	*6%*	*6%*	*6%*	*6%*
IBS-C treated patients	770	770	771	772	804	851	898	930	978	979
Linaclotide penetration	*0%*	*0%*	*0%*	*0%*	*0%*	*10%*	*20%*	*32%*	*38%*	*40%*
Patients on Linaclotide	0	0	0	0	0	85	180	298	371	391
Cost per month	$0	$0	$0	$116	$116	$116	$116	$116	$116	$116
Duration of therapy	0	0	0	0	3	4	5	6	6.5	6.5
Revenue per patient	$0	$0	$0	$0	$347	$462	$578	$693	$751	$751
Total EU IBS-C sales	$0	$0	$0	$0	$0	$39,311	$103,741	$206,257	$278,886	$293,858

Source: Company data, Morgan Stanley Research

Debate 3: Will Chronic Constipation Develop into a Large Market?

Chronic constipation (defined as fewer than three bowel movements per week) is a bigger market than IBS-C in terms of absolute patient numbers (affects ~30mn people in the US vs. IBS-C's ~11mn). However, a key question, and the swing factor that could determine whether linaclotide is a $1bn or $2bn+ drug, is how big of a commercial opportunity will this indication prove to be. While the market size is large, we expect penetration to be limited.

Exhibit 17

Linaclotide met its primary endpoint in two Phase III trials in chronic constipation

	Linaclotide		
	133 mcg	266 mcg	Placebo
LIN MD 01 Trial	N = 213	N = 202	N = 215
Primary Endpoint			
12-Week CSBM Overall Responder	34 (16.0%) p = 0.0012	43 (21.3%) p < 0.0001	13 (6.0%)
Secondary Endpoints			
Overall CSBM Rate Change ≥ 1	105 (49.3%) p < 0.0001	115 (56.9%) p < 0.0001)	55 (25.6%)

Source: Company data

Two Positive Phase III trials suggest linaclotide approval in chronic constipation

Ironwood and Forest have completed two Phase III trials for linaclotide in CC. These two trials both met the primary endpoint of proportion of complete spontaneous bowel movement overall responders as well as all secondary endpoints including bloating, abdominal discomfort, stool consistency, straining etc. The only notable side effect was diarrhea. We believe these data are adequate for US approval in this indication. The company does not plan to file for EU regulatory approval in this indication at this time.

Market could be difficult to access—expect limited penetration

Though a large market in terms of patient numbers, penetrating CC could be quite challenging. There are a number of relatively effective over-the-counter options for CC and patient urgency is less than IBS-C as abdominal discomfort is less severe. In addition, due the meaningful number of over-the-counter options and lack of disease severity reimbursement and physician acceptance may be challenging.

A key issue for US sales in this indication will be formulary placement and prior authorization. Given the potential size of this market and the number of cheap alternatives, third party payers may attempt to limit access by requiring prior authorization, etc.

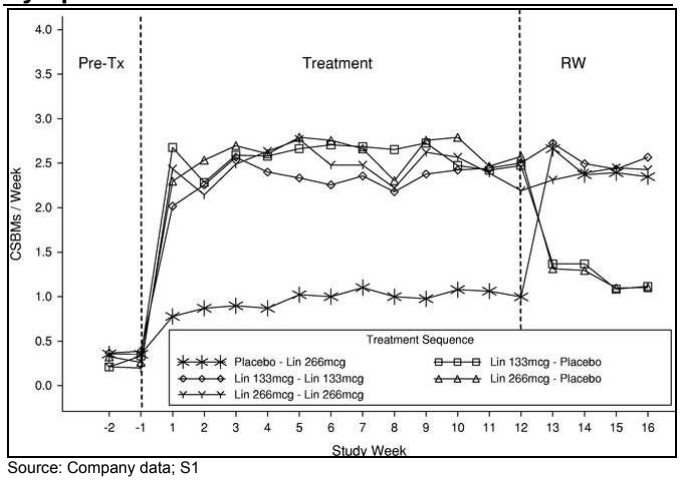
We assume peak penetration in CC of <1% overall (<15% of patients seeking care and unsatisfied with current treatments) with peak sales of ~$450mn.

Duration of therapy likely less in chronic constipation as well

A key driver of linaclotide sales will be compliance and how long patients stay on the drug. As discussed above, data to date do show that once patients stop taking drug, symptoms return to baseline levels quite rapidly (Exhibit 18). While these data suggest patients should continue taking the drug, in a disease area like chronic constipation, where symptoms may be tolerable for a length at a time, we expect patients are more likely to take the drug on a PRN (as needed) basis. In IBS-C, given the pain and abdominal discomfort involved, we model a peak average duration of 6.5 months; however, in chronic constipation, where symptoms are somewhat easier to tolerate, we model peak ***average*** duration of ~4 months as it is likely patients will take the drug intermittently, rather than on a continuous basis.

Exhibit 18

Drug cessation leads to rapid return of baseline symptoms



Source: Company data; S1

For comparison, prior to withdrawal from the market, Zelnorm reached an average duration of therapy between 90 and 110 days. Prilosec, on the other hand, an effective and relatively safe treatment for gastroesophageal reflux disease, has an average duration of therapy >190 days. Linaclotide, in our opinion, is a better drug than Zelnorm with stronger efficacy

and fewer side effects, thus we expect duration for linaclotide in IBS-C will be significantly more than the 90-110 observed with Zelnorm and is likely to approach an average duration similar to that observed with Prilosec. In chronic constipation, however, given the milder nature of the disease, we expect duration close to 100 days.

Marketing message will be key

Based on our discussion with management, we would not be surprised if the company tried to re-define the market away from IBS-C and CC and toward a more simple message – "If you have constipation and discomfort or pain, and you have failed everything else, try linaclotide." If the company is successful in re-defining the market toward this more simple message, we see several optimistic potential outcomes: 1) reimbursement hurdles may become less, as the company will be self-defining its place as a last line agent and 2) peak sales may be greater, as patients move away from treating constipation and toward treating pain and discomfort (a higher value proposition).

Exhibit 19

Chronic constipation market may prove more challenging than IBS-C

US Chronic Constipation	2008	2009	2010E	2011E	2012E	2013E	2014E	2015E	2016E	2017E
US Population	304,059	307,100	311,706	316,382	321,127	325,944	330,833	335,796	340,833	345,945
% with CC symptoms	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
US CC population	60812	61420	62341	63276	64225	65189	66167	67159	68167	69189
% seeking treatment for constipation	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
CC patients seeking treatment	12162	12284	12468	12655	12845	13038	13233	13432	13633	13838
% diagnosed with CC (not IBS-C/other G	50%	50%	50%	50%	50%	51%	51%	52%	52%	53%
CC treated patients	6081	6142	6234	6328	6423	6584	6749	6917	7089	7265
% on treatment and satisfied	55%	55%	55%	55%	55%	55%	55%	55%	55%	55%
Linaclotide eligible population	2737	2764	2805	2847	2890	2963	3037	3113	3190	3269
Linaclotide penetration	0%	0%	0%	0%	1%	2%	6%	10%	13%	15%
Patients on Linaclotide	0	0	0	0	29	59	167	311	415	484
Cost per month	0	0	0	210	214	218	223	227	232	236
Duration of therapy	0	0	0	0	3	3	3.5	4.0	4.0	4.0
Revenue per patient	$0	$0	$0	$0	$536	$655	$780	$909	$927	$946
Total US CC Sales	$0	$0	$0	$0	$15,477	$38,840	$130,287	$283,032	$384,628	$457,701

Source: Company data, Morgan Stanley Research

Debate 4: How and When Will the Company Build a Deeper Pipeline to Support its Significant Top-line Potential?

Linaclotide is Ironwood's only late-stage asset and though it has potential to generate significant cash flows, the long-term sustainability of the business depends on Ironwood's ability to build a pipeline behind linaclotide. Investors will likely continue to question the long-term growth potential and concentrated risk until there is notable progress with the earlier stage pipeline.

We cannot really offer an answer for this debate. We like management's track record , and feel confident that if they cannot find reasonable investments, they will return cash aggressively to shareholders.

Spend on basic research is limited
Ironwood currently spends <50% of its R&D budget on basic research (~$30mn of the $70mn total R&D in 2009). The company believes that it can innovate and sustain its top-line with this level of investment. Numerous companies have spent billions and found little. Alternative, there are a number of innovative biotech/emerging pharmaceutical companies that have spent little and then reached a wall post approval of a drug. Most have had to turn to external licensing and acquisitions.

Ironwood has a limited track record. It has brought one other drug into human testing, a Zetia-like compound for the treatment of hypercholesterolemia. The compound was safe and efficacious, but it showed no differentiation from Zetia, and especially with Zetia's ongoing safety and efficacy questions, the company decided to kill the drug during Phaes II development. We view this decision as a positive, as it showed that the company was willing to make the difficult early termination decision.

However, investors will need to watch for the emergence of a pipeline over the next few years. The company's R&D spend is clearly sub-industry norm. We would argue that over the next several years it will need to increase meaningfully in order to sustain a pipeline of drugs capable of sustaining the long-term growth investors will expect if we are correct on linaclotide's earnings power.

The company does have several late-stage, undisclosed pre-clinical assets and a novel pain drug in Phase I. Its research team has created several novel drugs (including linaclotide). We expect investors will give the company 3-6 years to develop at least a mid-stage pipeline, as the company does not have the capital to be an aggressive competitor for eternal assets. If the company has not created a pipeline by this time, investors may start to push for more early-to-mid stage assets or for the company to consider other strategic alternatives.

Reinvestment decisions will impact multiple
Ironwood does not have a proven track record of success in building pipelines and this could drag on the multiple until the company makes progress with another pipeline candidate. Long-term growth will depend on the company's ability to reinvest its cash flows in a way that either drives growth organically or via strategic actions.

We give no value to current early stage pipeline
Ironwood has one other drug candidate in clinical testing, IW-6118, an inhibitor of Fatty Acid Amide Hydrolase (FAAH). This drug is being evaluated for treatment of pain and inflammation. FAAH metabolizes bioactive lipid molecules, known as fatty acid amides, which have analgesic and anti-inflammatory properties. In a Phase I study, IW-6118 demonstrated favorable pharmacokinetics and dose-related elevation in biomarkers (FAA) suggesting IW-6118 is indeed inhibiting FAAH in humans. We currently give no value to this pipeline agent as data are early and limited to date, and pain has been a notoriously difficult indication to pursue.

Ironwood is also conducting early stage, preclinical research on ~8 therapeutic targets in gastrointestinal pain, inflammation and cardiovascular indications.

New investors have minority vote
Management and a small group of investors have controlling interest in the company. Ironwood has a dual class share structure (at least until Dec 31,2018) in which each share of Class A and Class B common stock has one vote per share expect on the following matters, where each share of **Class B common stock has 10 votes per share**: 1) adoption of a merger or consolidation agreement involving Ironwood; 2) a sale of all or substantially all of Ironwood's assets; 3) a dissolution or liquidation of Ironwood; 4) every matter if and when any individual, entity or group, has an intent to have beneficial ownership of 30% or more of the number of outstanding shares of Class A common stock and Class B common stock combined. Given that only management, the board, and a few large shareholders own Class B shares, these constituents have a strong say in the future

independence of the company. CEO Peter Hecht controls ~4.5% of the vote (which may increase if private investors sell), management and the board control ~30% of the vote, and management and any of the top 3 shareholders control enough of the vote to override the rest of shareholders.

New investors will only have a minority influence and therefore will have to trust management, the board, and a small group of investors to make the right decisions. Investors will need to continue to ask the question of whether management is reinvesting cash flows wisely and making appropriate strategic decisions, but at the present time, the question is nearly impossible to answer. To date, the track record appears strong.

Exhibit 20

Annual Income Statement

	2008	2009	2010E		2011E		2012E		2013E		2014E		2015E		2016E		2017E
Total Sales	**$0**	**$0**	**$0**		**$0**		**$97,380**		**$288,844**		**$644,717**		**$1,124,202**		**$1,472,701**		**$1,692,465**
Linaclotide US Sales	$0	$0	$0		$0		$97,380		$249,534		$540,977		$902,459		$1,158,969		$1,313,070
Linaclotide EU Sales	$0	$0	$0		$0		$0		$39,311		$103,741		$206,257		$278,886		$293,858
Linaclotide Japan and other Astellas terri	$0	$0	$0		$0		$0		$0		$0		$15,486		$34,845		$85,537
US profit split revenue	$0	$0	$0		$0		$2,866		$69,687		$201,372		$369,811		$495,252		$564,768
EU royalty	$0	$0	$0		$0		$0		$7,076		$25,935		$57,752		$83,666		$88,157
Japan/other royalty	$0	$0	$0		$0		$0		$0		$0		$2,633		$6,272		$15,397
Collaborative arrangement (Forest)	$18,383	$24,967	$24,967		$34,967		$99,000		$0		$0		$25,000		$25,000		$25,000
Collaborative arrangement (Almirall)	$0	$8,000	$8,000		$14,667		$29,667		$29,667		$0		$0		$0		$0
Collaborative arrangement (Astellas)		$410	$4,918		$4,918		$9,918		$9,918		$24,918		$20,000		$0		$0
Total Collaborative Revenue		**$33,896**	**$37,987**		**$54,551**		**$138,585**		**$39,585**		**$24,918**		**$45,000**		**$25,000**		**$25,000**
Services	$3,833	$1,981	$950		$380		$152		$0		$0		$0		$0		$0
Manufacturing Revenue		0	0		0		$0		$4,717		$11,204		$24,134		$30,955		$38,475
Total Revenue	$22,216	$35,877	$38,937		$54,931		$141,602		$121,065		$263,429		$499,329		$641,144		$731,797
Operating Expenses:																	
Cost of Sales	$0	$0	$0		$0		$4,869		$15,160		$32,328		$56,210		$72,154		$84,585
% total product sales	NA	NA	NA		NA		*5.0%*		*5.2%*		*5.0%*		*5.0%*		*4.9%*		*5.0%*
R&D	$58,101	$70,324	$54,000		$52,700		$52,980		$59,052		$60,862		$69,242		$75,666		$82,733
% of revenue	*262%*	*196%*	*139%*		*96%*		*37%*		*49%*		*23%*		*14%*		*12%*		*11%*
SG&A	$17,243	$25,309	$34,700	37%	$47,421	37%	$135,891	187%	$144,664	6%	$152,088	5%	$151,767	0%	$136,003	-10%	$140,866
% of revenue	*78%*	*71%*	*89%*		*86%*		*96%*		*119%*		*58%*		*30%*		*21%*		*19%*
Total Operating Expenses	$75,344	$95,633	$88,700		$100,121		$193,740		$218,876		$245,279		$277,218		$283,823		$308,184
Operating Income (Loss)	($53,128)	($59,756)	($49,763)		($45,190)		($52,138)		($97,810)		$18,150		$222,111		$357,321		$423,614
Operating Margin	NA	NA	NA		*-82%*		*-37%*		*-81%*		*7%*		*44%*		*56%*		*58%*
Interest, Other Income	$2,125	$244	$305		$3,309		$4,460		$5,124		$4,454		$9,942		$19,276		$29,621
Interest, Other Expense	($334)	($490)	($360)		($111)		$0		$0		$0		$0		$0		$0
Gain (loss) on forward purchase contract	($900)	($100)	-		-		-		-		-		-		-		-
Pretax Income (Loss)	($51,080)	($58,119)	($49,818)		($41,992)		($47,678)		($92,686)		$22,604		$232,053	927%	$376,598	62%	$453,235
Provision for Income Taxes	$0	($153)	$0		$0		$0		$0		$512		$8,839		$73,049		$145,500
Effective Tax Rate	*0%*	0%	0%		0%		0%		0%		4%		4%		20%		33%
Fully taxed net income	($32,691)	($37,196)	($31,884)		($26,875)		($30,514)		($59,319)		$14,467		$148,514		$241,022		$290,070
Net Income (Loss)	($51,080)	($57,966)	($49,818)		($41,992)		($47,678)		($92,686)		$22,092		$223,214		$303,549		$307,735
EPS, basic	($0.69)	($0.61)	($0.53)		($0.43)		($0.47)		($0.87)		$0.20		$2.01		$2.66		$2.62
EPS, diluted	($0.69)	($0.61)	($0.53)		($0.43)		($0.47)		($0.87)		$0.19		$1.90		$2.55		$2.56
EPS, diluted, fully taxed	($0.44)	($0.39)	($0.34)		($0.27)		($0.30)		($0.56)		$0.13		$1.27		$2.03		$2.42
EPS, diluted (incl. options expense)	($0.72)	($0.66)	($0.57)		($0.47)		($0.54)		($0.96)		$0.11		$1.81		$2.48		$2.49
Basic Shares Outstanding	74,495	94,396	94,396		98,284		101,911		105,968		108,549		111,296		114,209		117,297
Diluted Shares Outstanding	74,495	94,396	94,396		98,284		101,911		105,968		115,523		117,340		118,899		120,084

Source: Company data, Morgan Stanley Research

Exhibit 21

Balance Sheet

	2008	2009	2010E	2011E	2012E	2013E	2014E	2015E	2016E	2017E
Assets										
Cash and cash equivalents	$67,722	$82,218	$209,611	$147,468	$204,479	$131,365	$170,857	$498,103	$849,732	$1,250,465
Available-for-sales securities	$22,045	$32,045	$37,045	$47,045	$47,045	$27,045	$27,045	$27,045	$27,045	$27,045
Accounts receivable	$6,923	$7,175	$5,841	$8,240	$21,240	$12,107	$26,343	$44,940	$57,703	$65,862
Related party accounts receivable	$198	$99	$50	$25	0	0	0	0	0	0
Prepaid expenses and other assets	$2,498	$3,588	$3,894	$4,944	$11,328	$7,264	$13,171	$24,966	$32,057	$36,590
Forward purchase contract	$8,700	0	0	0	0	0	0	0	0	0
Total current assets	**$108,086**	**$125,125**	**$256,440**	**$207,721**	**$284,093**	**$177,781**	**$237,417**	**$595,054**	**$966,537**	**$1,379,961**
Restricted cash	$7,968	$7,968	$7,968	$7,968	$7,968	$7,968	$7,968	$7,968	$7,968	$7,968
Property and equipment, net	$24,596	$26,496	$27,260	$27,882	$28,360	$28,687	$28,861	$28,878	$28,733	$28,646
Forward purchase contract (non-current)	-	-	-	-	-	-	-	-	-	-
Other assets	$73	$73	$73	$73	$73	$73	$73	$73	$73	$73
Total assets	**$140,723**	**$159,662**	**$291,740**	**$243,644**	**$320,494**	**$214,509**	**$274,319**	**$631,973**	**$1,003,312**	**$1,416,649**
Liabilities and stockholders' equity										
Accounts payable	$6,086	$7,651	$7,096	$8,510	$17,437	$19,699	$24,528	$27,722	$31,221	$33,900
Accrued research and development costs	$9,653	$9,845	$7,560	$6,851	$6,887	$7,677	$7,912	$9,001	$9,837	$10,755
Accrued expenses	$4,507	$5,738	$5,766	$7,008	$13,562	$17,510	$19,622	$22,177	$22,706	$24,655
Current portion of LT debt	$943	$2,681	$2,191	$0	$0	$0	$0	$0	$0	$0
Current portion of capital lease obligations	$117	$117	$72	$0	$0	$0	$0	$0	$0	$0
Deferred revenue (current)	$17,846	$37,885	$37,885	$33,585	$34,585	$9,918	$5,000	$0	$0	$0
Total current liabilities	**$39,152**	**$63,917**	**$60,569**	**$55,954**	**$72,471**	**$54,804**	**$57,062**	**$58,901**	**$63,763**	**$69,310**
Long-term debt, net of current portion	$872	$2,191	$0	$0	$0	$0	$0	$0	$0	$0
Captial lease obligations, net of current	$189	$72	$0	$0	$0	$0	$0	$0	$0	$0
Deferred rent	$9,313	$8,149	$6,985	$5,821	$4,657	$3,492	$2,328	$1,164	$0	$0
Deferred revenue (non-current)	$48,208	$84,793	$46,908	$36,657	$27,072	$5,000	$0	$75,000	$50,000	$25,000
Minority interest	$5,339	$5,339	$0	$0	$0	$0	$0	$0	$0	$0
Total liabilities	**$103,073**	**$164,460**	**$114,462**	**$98,432**	**$104,199**	**$63,296**	**$59,391**	**$135,065**	**$113,763**	**$94,310**
Preferred stock	$67	$67	0	0	0	0	0	0	0	0
Common stock plus Additional paid-in capital	$280,934	$300,452	$535,961	$549,892	$676,401	$712,761	$763,803	$833,214	$931,388	$1,064,701
Accumulated deficit	($243,374)	($305,340)	($358,706)	($404,703)	($460,130)	($561,571)	($548,897)	($336,328)	($41,862)	$257,614
Accumulated other comprehensive income	$23	$23	$23	$23	$23	$23	$23	$23	$23	$23
Total stockholders' equity	**$37,650**	**-$4,798**	**$177,278**	**$145,212**	**$216,295**	**$151,213**	**$214,929**	**$496,908**	**$889,549**	**$1,322,338**
Total liabilities and stockholder's equity	**$140,723**	**$159,662**	**$291,740**	**$243,644**	**$320,494**	**$214,509**	**$274,319**	**$631,973**	**$1,003,312**	**$1,416,649**

Source: Company data, Morgan Stanley Research

Exhibit 22

Cash Flow Statement

	2008	2009	2010E	2011E	2012E	2013E	2014E	2015E	2016E	2017E
Net loss	($53,874)	($61,966)	($53,366)	($45,997)	($55,427)	($101,441)	$12,674	$212,569	$294,466	$299,476
Depreciation and amortization	$2,849	$3,095	$3,231	$3,372	$3,518	$3,667	$3,821	$3,979	$4,140	$4,082
Gain on disposal of PPE	($1)	$0	$0	$0	$0	$0	$0	$0	$0	$0
Minority interest	($1,157)	$0	($5,339)	$0	$0	$0	$0	$0	$0	$0
Remeasurement of forward purchase contract	$900	$8,700	$0	$0	$0	$0	$0	$0	$0	$0
Stock-based compensation expense	$2,794	$4,000	$3,548	$4,005	$7,750	$8,755	$9,419	$10,645	$9,082	$8,259
Accretion of discount/premium on investment securities	($368)	$0	$0	$0	$0	$0	$0	$0	$0	$0
Accounts receivable	$18,183	($252)	$1,335	($2,399)	($13,001)	$9,134	($14,236)	($18,597)	($12,763)	($8,159)
Related party accounts receivable	$204	$99	$50	$25	$25	$0	$0	$0	$0	$0
Resticted cash	($5,008)	$0	$0	$0	$0	$0	$0	$0	$0	$0
Prepaid expenses and other current assets	($768)	($1,090)	($306)	($1,050)	($6,384)	$4,064	($5,908)	($11,795)	($7,091)	($4,533)
Other assets	($45)	$0	$0	$0	$0	$0	$0	$0	$0	$0
Accounts payable and accured expenses	$2,507	$2,796	($527)	$2,657	$15,480	$6,210	$6,941	$5,749	$4,027	$4,629
Accrued research and development costs	$4,615	$192	($2,285)	($709)	$36	$789	$235	$1,089	$835	$919
Deferred revenue	($8,338)	$56,623	($37,885)	($14,551)	($8,585)	($46,739)	($9,918)	$70,000	($25,000)	($25,000)
Long-term deferred rent	$9,313	($1,281)	($1,281)	($1,236)	($1,164)	($1,164)	($1,164)	($1,164)	($1,164)	$0
Net cash used in operating activities	**($28,194)**	**$10,916**	**($92,826)**	**($55,883)**	**($57,753)**	**($116,724)**	**$1,864**	**$272,475**	**$266,532**	**$279,673**
Investing Activities:										
Purchases of available-for-sale securities	($82,613)	($30,000)	($25,000)	($20,000)	$0	$0	$0	$0	$0	$0
Sales and maturities of available-for-sale securities	$90,465	$20,000	$20,000	$10,000	$0	$20,000	$0	$0	$0	$0
Purchases of PPE	($22,934)	($5,000)	($4,000)	($4,000)	($4,000)	($4,000)	($4,000)	($4,000)	($4,000)	($4,000)
Proceeds from the sale of PPE	$9	$5	$5	$5	$5	$5	$5	$5	$5	$5
Net cash used in investing activities	**($15,073)**	**($14,995)**	**($8,995)**	**($13,995)**	**($3,995)**	**$16,005**	**($3,995)**	**($3,995)**	**($3,995)**	**($3,995)**
Financing activities:										
Proceeds from issuance of preferred stock, net of issuance costs	$49,598	$0	$25,000	$0	$0	$0	$0	$0	$0	$0
Proceeds from issuance of common stock		$15,000	$203,000	$0	$100,000	$0	$0	$0	$0	$0
Proceeds from exercise of stock options	$179	$518	$3,894	$9,926	$18,760	$27,605	$39,875	$57,062	$81,655	$116,849
Tax benefit from stock options	$0	$0	$0	$0	$0	$0	$1,748	$1,704	$7,436	$8,206
Proceeds from borrowings	$465	$6,000	$0	$0	$0	$0	$0	$0	$0	$0
Payments on borrowings	($1,680)	($2,943)	($2,681)	($2,191)	$0	$0	$0	$0	$0	$0
Net cash provided by financing activities	**$48,562**	**$18,575**	**$229,213**	**$7,735**	**$118,760**	**$27,605**	**$41,623**	**$58,765**	**$89,092**	**$125,054**
Increase in cash and cash equivalents	$5,295	$14,496	$127,393	($62,143)	$57,012	-$73,114	$39,492	$327,246	$351,629	$400,733
Cash and equivalents at beginning of year	$62,427	$67,722	$82,218	$209,611	$147,468	$204,479	$131,365	$170,857	$498,103	$849,732
Cash and equivalents at end of year	**$67,722**	**$82,218**	**$209,611**	**$147,468**	**$204,479**	**$131,365**	**$170,857**	**$498,103**	**$849,732**	**$1,250,465**

Source: Company data, Morgan Stanley Research

Company Description

Ironwood is a pharmaceutical company that discovers, develops, and intends to commercialize innovative medicines targeting important therapeutic needs. Ironwood's lead drug candidate Linaclotide, a first-in-class compound for treatment of patients with irritable bowel syndrome with constipation or chronic constipation, is currently in Phase III development.

MORGAN STANLEY ModelWare	**Morgan Stanley ModelWare is a proprietary analytic framework that helps clients uncover value, adjusting for distortions and ambiguities created by local accounting regulations.** For example, ModelWare EPS adjusts for one-time events, capitalizes operating leases (where their use is significant), and converts inventory from LIFO costing to a FIFO basis. ModelWare also emphasizes the separation of operating performance of a company from its financing for a more complete view of how a company generates earnings.

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Global Stock Ratings Distribution

(as of February 28, 2010)

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	Coverage Universe		Investment Banking Clients (IBC)		
Stock Rating Category	Count	% of Total	Count	% of Total IBC	% of Rating Category
Overweight/Buy	**1035**	**41%**	**316**	**42%**	**31%**
Equal-weight/Hold	**1091**	**43%**	**341**	**45%**	**31%**
Not-Rated/Hold	**22**	**1%**	**5**	**1%**	**23%**
Underweight/Sell	**382**	**15%**	**89**	**12%**	**23%**
Total	**2,530**		**751**		

Data include common stock and ADRs currently assigned ratings. An investor's decision to buy or sell a stock should depend on individual circumstances (such as the investor's existing holdings) and other considerations. Investment Banking Clients are companies from whom Morgan Stanley or an affiliate received investment banking compensation in the last 12 months.

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Overweight (O). The stock's total return is expected to exceed the average total return of the analyst's industry (or industry team's) coverage universe, on a risk-adjusted basis, over the next 12-18 months.
Equal-weight (E). The stock's total return is expected to be in line with the average total return of the analyst's industry (or industry team's) coverage universe, on a risk-adjusted basis, over the next 12-18 months.
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Unless otherwise specified, the time frame for price targets included in Morgan Stanley Research is 12 to 18 months.

Analyst Industry Views

Attractive (A): The analyst expects the performance of his or her industry coverage universe over the next 12-18 months to be attractive vs. the relevant broad market benchmark, as indicated below.
In-Line (I): The analyst expects the performance of his or her industry coverage universe over the next 12-18 months to be in line with the relevant broad market benchmark, as indicated below.
Cautious (C): The analyst views the performance of his or her industry coverage universe over the next 12-18 months with caution vs. the relevant broad market benchmark, as indicated below.
Benchmarks for each region are as follows: North America - S&P 500; Latin America - relevant MSCI country index or MSCI Latin America Index; Europe - MSCI Europe; Japan - TOPIX; Asia - relevant MSCI country index.
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Industry Coverage:Biotechnology

Company (Ticker)	Rating (as of)	Price* (03/12/2010)
Steven Harr, M.D.		
Ironwood Pharmaceuticals (IRWD.O)	O (03/15/2010)	$12.91
Affymax Inc (AFFY.O)	E (01/29/2009)	$20.75
Amgen (AMGN.O)	O (07/28/2008)	$57.43
Amicus (FOLD.O)	E (12/20/2007)	$3.43
Amylin Pharmaceuticals (AMLN.O)	E (10/27/2008)	$20.26
Biocryst Pharmaceuticals, Inc. (BCRX.O)	E (12/21/2009)	$7.35
Biogen Idec (BIIB.O)	U (07/30/2007)	$58.76
Celgene Corporation (CELG.O)	O (09/10/2009)	$61.37
Genzyme Corporation (GENZ.O)	U (12/21/2009)	$56.91
Gilead Sciences, Inc. (GILD.O)	E (09/10/2009)	$47.42
Human Genome Sciences Inc. (HGSI.O)	O (12/21/2009)	$32.64
OSI Pharmaceuticals (OSIP.O)	O (08/13/2002)	$57.68
Onyx Pharmaceuticals (ONXX.O)	U (10/27/2008)	$30.86
Regeneron (REGN.O)	E (06/05/2008)	$24.69
Vertex Pharmaceuticals (VRTX.O)	O (11/04/2009)	$43.46
XenoPort (XNPT.O)	E (02/18/2010)	$8.48
Marshall Urist, M.D., Ph.D.		
AMAG Pharmaceuticals, Inc. (AMAG.O)	E (11/16/2007)	$35.98
Auxilium Pharmaceuticals (AUXL.O)	O (11/16/2007)	$34.41

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