IRONWOOD PHARMACEUTICALS (NASDAQ: IRWD)

Trailblazing New Markets in Gastroenterology.
Initiating Coverage with a BUY Rating and $14.00 Price Target.

Investment Rating	BUY
Price Target	$14.00
Price (9/07/10)	$9.27
52 Week Range	$9.05 - $15.03
Shares Outstanding	97.6 MM
Market Capitalization	$905 MM
Cash (6/30/10)	$271.6 MM
Enterprise Value	$633.2 MM
Avg. Volume	224,000
S&P 500 Index (9/07/10)	1,092
NASDAQ Composite (9/07/10)	2,209

FY (Dec)	2009A	2010E	2011E
Revs. (MM)	$36.1	$39.1	$38.6
Net Inc. (MM)	($71.5)	($68.7)	($46.0)
EPS	($10.00)	($0.77)	($0.47)

EPS (Qtr.)	Mar	Jun	Sept	Dec
2010E	($0.25) A	($0.18) A	($0.20)	($0.16)
2011E	($0.15)	($0.12)	($0.10)	($0.10)

Company Description

IRWD is a biopharmaceutical company primarily focused on developing and commercializing of linaclotide for the treatment of IBS-C and CC. Linaclotide is partnered with FRX in the US and Phase III results in IBS-C are expected in Q4 2010. Phase III Results in CC were released and found to be positive.

Highlights

We are initiating coverage of IRWD with a BUY rating and a risk-adjusted price target of $14.00. Our positive opinion is based on our belief that linaclotide (based on its safety profile, rapid onset of action and an adequate relief of multiple abdominal IBS-C symptoms) will likely become the gold standard for the treatment of IBS-C. We believe, if granted a label claiming abdominal pain benefit, linaclotide could become a commercial success with blockbuster potential.

It is also our belief the Street is underestimating the probability of both clinical trials to meet all of the three co-primary endpoints. In addition, we believe meeting the key endpoint of abdominal pain is a lower hurdle than the Street's expectations.

We also believe the Street is underestimating the size of the market potential for linaclotide. We believe linaclotide has the potential to become a >$1.3 billion million product in the US and a $300 million product between Europe and Asia.

In addition, if effects in abdominal pain and bloating are strong and persistent, we expect the long-term value of the drug to be enhanced (beyond IBS-C) its potential in other abdominal conditions such as dyspepsia, gastroparesis, mixed-IBS, and others. Given the size of these patient populations and the prevalence of abdominal pain and bloating, we envision linaclotide generating significant additional revenues vs. our current forecast (>30%). (Not included in our valuation model.)

Linaclotide is a first in class drug that offers symptomatic benefit (pain and bloating) which is not obtained with existing therapies and faces limited competition in a large market (>40 million patients). In addition, linaclotide data available to date has demonstrated a pristine safety profile. We see this characteristic as of key importance for a drug which will potentially be prescribed chronically in a wide patient population and by many physicians, including primary care practitioners.

Linaclotide is partnered with Forest Labs (NYSE: FRX; not rated; $29.45) in North America in a 50:50 development and commercialization collaboration. The US pivotal program consists of two pivotal trials in chronic constipation (CC) (already reported and positive) and two pivotal trials in IBS-C (results due Q4 2010).

The European regulatory program (partnered with Almirall S.A) focuses on IBS-C only and timelines are few months behind the US program. The European filing will use the same IBS-C pivotal trials for regulatory filing (although with different endpoints and statistical analyses).

Upside and downside: We believe positive results in the Phase III IBS-C results should value IRWD shares in the $18.00 -$19.00 range (assuming data is strong), mixed or negative data in the $5.00 level. Our price target of $14.00 is derived from a risk-adjusted valuation methodology (pre-pivotal trials data).

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Disclosures and Analyst Certifications can be found in Appendix A.

Table 1. Upcoming Milestones

Timing	Event
Q4 2010	Linaclotide Phase III Clinical Trial Results in IBS-C
2H 2011	Linaclotide NDA Filing in the US
2H 2011	Linaclotide Filing in Europe
2H 2012	Potential US Approval
2H 2010 / 1H 2013	Potential European Approval

Source: Corporate Presentations and Ladenburg Thalmann & Co. estimates

Initiating coverage of IRWD with a BUY rating and a risk-adjusted price target of $14.00.

We view linaclotide as the first drug with the potential to offer significant and sustained relief from abdominal pain and bloating to patients with IBS-C (irritable bowel syndrome-constipation only) and potentially other similar conditions. Although we believe available therapies (OTC and prescription medicines) for IBS-C do a proper job at treating constipation symptoms (straining, complete spontaneous bowel movement (CSBM), stool consistency) in some patients, they are mediocre (almost useless) at treating abdominal symptoms (pain, bloating, discomfort).

Linaclotide (agonist of guanylate cyclase type-C) is a first-in-class drug addressing a large market of over 12 million patients with IBS-C and 34 million with chronic constipation (CC) with an existing medical need (in abdominal pain and bloating) and limited competition (few prescription medicines available and efficacy of existing drugs are limited).

In addition, we believe linaclotide's benign safety profile and rapid and sustained effect could allow adoption by many physician groups (including primary care practitioners) and chronic usage by a wide patient population.

IBS-C, due to the predominance of abdominal symptoms, represents the first significant target market segment for linaclotide. At the moment, we don't see CC as a significant market opportunity due to the low prevalence of abdominal symptoms in these patients.

In Phase IIb clinical studies in IBS-C, over 60% of patients obtained significant response (an improvement of 0.5 points in a 1-5 scale is considered clinically significant in this setting) in abdominal pain, discomfort and bloating, individually. In addition, 68% of patients reported obtaining adequate relief during therapy with linaclotide. We expect the two ongoing Phase III clinical trials to confirm prior findings and to render positive results.

In our view, these response rates are extremely high for a symptomatic pharmaceutical compound and are part of the basis of our confidence linaclotide will become a major blockbuster.

We believe linaclotide has the potential to become a $1.3 billion million product in the US and a $300 million product between Europe and Asia.

We estimate under the linaclotide profit share agreement with FRX, net profits for IRWD could surpass $450 million at peak. In case the linaclotide pivotal trial is negative and/or a pain (or IBS-C) claim is not obtained, we estimate net profits for IRWD could approximate $160 million before considering proactive measures by the FRX and IRWD.

Thus, we estimate positive linaclotide pivotal results could value IRWD at approximately $18.00 per share and mixed or negative data at $5.00 per share.

Assuming successful pivotal trial results (Q4 2010 event), we expect the NDA filing in mid 2011 and potential approval (and commercial launch) in 2H 2012. The regulatory timelines for Europe run a few months behind the US.

IRWD ended Q2 2010 with $271.6 million in cash and the Company expects to end 2010 with over $220 million in cash. IRWD could receive up to $190 million clinical and regulatory milestones payments from its partners before the launch of linaclotide. As such, we estimate IRWD could have over $250 million in cash upon the potential approval of linaclotide (2H 2012).

Linaclotide's composition of matter patent expires in 2025 in the US and in 2024 in the European Union. Pediatric indications and Hatch-Watchman could provide protection until 2027.

In addition, IRWD filed a formulation patent application for orally delivered peptides and manufacturing claims which could extend market exclusivity. As is often the case with drugs with no (or poor) systemic absorption, the demonstration of bioequivalence is challenging for generic companies, potentially providing additional protection.

VALUATION

Initiating coverage of Ironwood (IRWD) with a BUY rating and a risk-adjusted price target of $14.00.

Our IRWD valuation is solely based on the prospects of linaclotide. In our estimates, the combined probability that both linaclotide pivotal studies meet each one of the three original co-primary endpoints is 66%. However, given the potential addition of a fourth endpoint and other considerations, we believe the overall probability of linaclotide obtaining a label claim for abdominal pain could be higher (See page 17 for discussion).

We use a relatively high valuation multiple (9x) to net profits (FRX agreement) and royalties as these profits are not associated with any significant cost from IRWD. With potential IP protection until 2027 and high profit margins, we believe a high valuation multiple is justified. Our model excludes potential upside from label expansion into indications such as dyspepsia, mixed IBS, gastroparesis, pediatric indications and others.

Table 2. IRWD Risk-Adjusted Sum-of-the-Parts Valuation Table ($000s)

Amounts in $000s	Peak Revenues ($) (est. 2016-2017)	IRWD Net Profit / Royalties	Multiple	Valuation (Present Value)*	Probability**	Probability Ajusted	Per Estimated Fully Diluted Share
North American Market	1,284,256	477,996	9.0x	1,888,832	66%	1,246,157	10.58
European Market	236,346	59,086	8.0x	207,541	72%	149,199	1.27
Asia	70,000	12,600	8.0x	41,542	66%	27,407	0.23
Other						20,000	0.17
Cash Expected at Approval (Excludes approval milestone payment)						160,000	
TOTAL	**1,590,602**					**1,602,763**	
Outstanding Shares (Class A)						19,167	
Outstanding Shares (Class B)						78,839	
						98,006	
Options						15,227	
Future Dilution						4,500	
Estimated Fully-Diluted Shares						117,733	
Valuation per Share						**13.61**	

** uses a 13.5% discount rate*

*** refers to the probability of regulatory approval and reaching our revenue estimates*

Source: Ladenburg Thalmann & Co. estimates

Downside Case: In the scenario linaclotide's pivotal trial is negative and/or a pain (or IBS-C) claim is not obtained, our model predicts linaclotide's P&L to become cash flow positive once revenues of approximately $200 million are reached. (This case does not take proactive measures which FRX and IRWD may be undertaken.) For this reason, in this downside case, IRWD's shares of profits would be relatively modest (~$160 million), setting a $5.00 valuation level.

Table 3. Sum-of-the-Parts Valuation Downside Case ($000s)

Amounts in $000s	Peak Revenues ($) (est. 2016)	IRWD Net Profit / Royalties	Multiple	Valuation (Present Value)*	Probability**	Probability Ajusted	Per Estimated Fully Diluted Share
North American Market	514,851	163,289	5.0x	381,903	90%	343,712	2.92
European Market	179,125	44,781	5.0x	92,277	90%	83,050	0.71
Asia	50,000	8,820	5.0x	18,175	60%	10,905	0.09
Other						10,000	0.08
Cash Expected at Approval (Excludes approval milestone payment)						100,000	
TOTAL	**743,976**			**492,355**		**547,667**	
Outstanding Shares (Class A)						19,181	
Outstanding Shares (Class B)						78,851	
						98,031	
Options						7,614	
Future Dilution						4,000	
Estimated Fully-Diluted Shares						109,645	
Valuation per Share						**4.99**	

** uses a 13.5% discount rate*
*** refers to the probability of regulatory approval and reaching our revenue estimates*
Source: Ladenburg Thalmann & Co. estimates

Upside Case (after positive Phase III IBS-C results): Under this scenario our model predicts linaclotide's P&L becomes the base case revenue estimates for linaclotide, but the probability of a successful outcome (due to positive clinical results) increases. We estimate IRWD shares could be valued at >$18.00 upon a strong positive Phase III IBS-C.

In addition, although not included in this valuation case, if the abdominal pain and bloating data is strong, long-term investors could begin to contemplate the potential of linaclotide outside of IBS-C and CC. In these circumstances, we believe US revenues could increase by >30% from our current projections.

Table 4. Upside Case Sum-of-Parts Valuation ($000s)

Amounts in $000s	Peak Revenues ($) (est. 2016)	IRWD Net Profit / Royalties	Multiple	Valuation (Present Value)*	Probability**	Probability Ajusted	Per Estimated Fully Diluted Share
North American Market	1,284,256	477,996	9.0x	1,888,832	90%	1,699,949	14.44
European Market	236,346	59,086	8.0x	194,808	90%	175,327	1.49
Asia	70,000	12,600	8.0x	41,542	70%	29,080	0.25
Other	-					20,000	0.17
Cash Expected at Approval (Excludes approval milestone payment)						270,000	
*Upside Off-Label and Future Indications****	*398,119*	*175,173*	*8.0x*	*1,401,380*	*50%*	*700,690*	*5.95*
TOTAL (Excluding upside)						**2,194,355**	**18.64**
TOTAL (Including Upside)	**1,590,602**					**2,875,046**	**24.42**
Outstanding Shares (Class A)						19,167	
Outstanding Shares (Class B)						78,839	
						98,006	
Options						15,227	
Future Dilution						4,500	
Estimated Fully-Diluted Shares						117,733	
Valuation per Share (excluding upside)						**18.64**	
Valuation per Share (including upside)						**24.42**	

** uses a 13.5% discount rate*
*** refers to the probability of regulatory approval and reaching our revenue estimates*
**** Exluded from valuation (for representative purposes only)*
Source: Ladenburg Thalmann & Co. estimates

Other Valuation Methodologies

We complement our sum-of-the-parts analysis with a P/E and DCF valuation analysis to better account for IRWD's operating infrastructure and long-term earnings potential. Our DCF and P/E models do not risk-adjust linaclotide's future revenues; therefore, these models describe IRWD's potential in the event linaclotide becomes the product described in our base case scenario.

P/E Multiple. We estimate IRWD could generate fully diluted EPS of $1.43, $2.77 and $3.28 in 2016, 2017 and 2018, respectively. Using appropriate P/E multiples (12x to 15x) and different discount rates, we estimate a valuation range of $15.00 to $21.00, which is compatible with our expectations in the sum-of-the-parts analysis.

Table 5. IRWD P/E Multiple Valuation Tables

2017

Discount Rate	Multiple on Fully Diluted EPS					
	8x	10x	12x	14x	15x	20x
	$22.17	$27.71	$33.25	$38.79	$41.56	$55.41
8.0%	$12.93	$16.17	$19.40	$22.63	$24.25	$32.33
10.0%	$11.37	$14.22	$17.06	$19.90	$21.33	$28.44
11.0%	$10.68	$13.35	$16.01	**$18.68**	**$20.02**	$26.69
12.0%	$10.03	$12.53	$15.04	**$17.55**	**$18.80**	$25.07
13.0%	$9.42	$11.78	$14.13	**$16.49**	**$17.67**	$23.55
14.0%	$8.86	$11.07	$13.29	$15.50	$16.61	$22.15
15.0%	$8.33	$10.42	$12.50	$14.58	$15.62	$20.83
16.0%	$7.84	$9.80	$11.76	$13.72	$14.71	$19.61
20.0%	$6.19	$7.73	$9.28	$10.83	$11.60	$15.46

2018

Discount Rate	Multiple on Fully Diluted EPS					
	8x	10x	12x	14x	15x	20x
	$26.20	$32.75	$39.30	$45.85	$49.13	$65.50
8.0%	$14.16	$17.69	$21.23	$24.77	$26.54	$35.39
10.0%	$12.22	$15.28	$18.33	$21.39	$22.92	$30.56
11.0%	$11.37	$14.21	**$17.05**	**$19.90**	**$21.32**	$28.42
12.0%	$10.58	$13.23	**$15.87**	**$18.52**	**$19.84**	$26.45
13.0%	$9.86	$12.32	**$14.78**	**$17.25**	**$18.48**	$24.64
14.0%	$9.18	$11.48	$13.78	$16.07	$17.22	$22.96
15.0%	$8.56	$10.71	$12.85	$14.99	$16.06	$21.41
16.0%	$7.99	$9.99	$11.99	$13.99	$14.98	$19.98
20.0%	$6.09	$7.62	$9.14	$10.66	$11.42	$15.23

Source: Ladenburg Thalmann estimates

Discounted Cash Flow Valuation:

Our DCF model implies a valuation for IRWD of $1.8 billion or $17.00 per fully diluted share. Our DCF methodology uses a WACC of 12.0% and perpetuity growth rate of 3.0%.

Table 6. IRWD Discounted Cash Flow Table ($000s)

		2011E	2012E	2013E	2014E	2015E	2016E	2017E	2018E
FCF		**($64,511)**	**$57,565**	**($138,481)**	**($109,876)**	**($15,101)**	**$111,589**	**$256,745**	**$346,685**
NPV		$124,019	$203,412	$170,257	$510,079	$681,165	$778,006	$759,778	$594,206
WACC	12%								
Perpetuity Growth Rate	3%								
NPV of Free Cash Flows 2012-2018	**$181,618**								
Terminal Value									
Terminal Value	**$3,967,615**								
Present Value of TV	**$1,794,747**								
Est Net Cash (End 2011)	$196,205								
Corporate Valuation	**$1,990,952**								
Shares Used	117,733								
Per Share	**$16.9**								

Source: Ladenburg Thalmann & Co. Estimates

The Forest Collaboration: In September 2007, IRWD and FRX signed a 50:50 co-development and co-commercialization collaboration for the North America market. IRWD received an upfront payment of $70 million.

Including upfront payments and contingent equity investments, IRWD could receive up to $330 million in development and commercial milestones (over the course of the collaboration) of which $125.0 million has already been received.

IRWD can opt to fund up to 35% of the linaclotide detailing with its own sales force and medical science liaisons (MSLs). IRWD is responsible for the linaclotide NDA and interactions with the FDA. In addition, there are strong non-compete, change of control, standstill, and termination provisions in the contract.

The Almirall Collaboration: In April 2009, IRWD and Almirall S.A. signed a license agreement for linaclotide's European rights. IRWD received an upfront payment of $38 million. Potential clinical and sales milestone payments and contingent equity investments could add up to $55 million.

IRWD is entitled to receive escalating royalties from European sales. We estimate IRWD can capture ≥50% of the economics of linaclotide in Europe. As such, we model long-term royalties of ≥25%.

The European Medicines Agency (EMA) agreed Almirall can use the US Phase III IBS-C trials as the basis for a market authorization application (MAA). The primary endpoint will be different and a separate statistical analysis will be performed. For this reason, we expect a MAA filing in mid 2011 and potential approval in 2H 2012.

The Astellas Pharma Collaboration: In November 2009, IRWD and Astellas Pharma signed an agreement for the development of linaclotide in Japan, South Korea, Taiwan, Thailand, Philippines and Indonesia. IRWD received an upfront payment of $30 million and could receive additional development milestone payments totaling up to $45 million, and escalating royalties on net sales.

We estimate the Asian regulatory program is >3 years behind the US and Europe.

Long-Term Cash Needs: IRWD has indicated it could receive up to $190 million in pre-commercialization milestones from various partners. We expect milestone payments from partners upon positive linaclotide pivotal trial results, NDA acceptance (a mid 2011 event) and FDA approval (a 2012 event).

IRWD ended Q2 2010 with $271.6 million in cash and expects to end 2010 with over $220 million in cash. If one assumes combined milestone payments of $30.0 million upon positive IBS-C results, IRWD's cash position by YE 2010 could reach $250 million.

In 2011, as expenses associated with linaclotide's pivotal program recede, we expect IRWD's expenses to approximate $85 million. In 2011, IRWD could receive milestone payments related to the NDA filing (or acceptance) in the US and MAA filing in Europe. In the presence of these milestones ($30 million in our model), we estimate IRWD could end FY 2011 with over $190 million in cash.

In 2012 we expect a potential linaclotide PDUFA date (and EMA decision date) by the middle of the year. IRWD has the option to fund up to 35% of linaclotide's detailing and medical science liaisons (MSLs) in the US, therefore we model IRWD hiring a sales force of 150 Reps (to then increase overtime) in mid 2012. Consequently, if linaclotide is approved in mid 2012, we estimate IRWD's cash position would be over $250 million taking regulatory milestone payments into consideration (however, this figure is contingent on the timing of European approval).

Post-approval: We do not expect the North America linaclotide P&L to become profitable until late 2014-2015. We estimate linaclotide's North American operations to become profitable with approximately $250-$260 million in revenues (if the label includes an abdominal pain claim) or with approximately $200 million in revenues (if the label does not include an abdominal pain claim).

In addition, we estimate royalty revenues coming from an early launch in Europe would be relatively small. Meanwhile, IRWD's base (ex-linaclotide) R&D and SG&A expenses would approximate $65-$80 million a year. In addition, we estimate IRWD's expenses associated with linaclotide (and not included in the linaclotide agreement with FRX) could initially approximate $13 million to then grow to ~$20 million.

In summary, we believe IRWD's cash position is solid and, coupled with future potential milestone payments, is sufficient to fund the Company's operations two years into the U.S. launch of linaclotide. In the event IRWD decides to undertake a significant strategic transaction (e.g. in-licensing a product to leverage sales force), we believe modest dilution would be necessary over the next five years.

Table 7. IRWD's Estimated Cash Balances ($000)

	2010E	2011E	2012E	2013E
Cash Balance (incl milestone payments)	255,805	196,205	232,247	119,637
Burn Rate	(45,800)	(84,600)	(98,958)	(112,610)
Milestone Payments	30,000	25,000	135,000	-

Source: Ladenburg Thalmann estimates

Looking for passive investors. IRWD has a dual class share structure (Class A and Class B common stock shares). Currently, there are 19.2 million outstanding Class A shares and 78.8 million outstanding Class B shares. Each Class B share has 10 votes (vs. one vote for Class A shares) on the following potential events: a merger agreement, liquidation of the Company, sale of IRWD assets, or in the event an individual or institution obtains more than 30% of outstanding shares (Class A and B combined).

Therefore, new investors will always have minority influence in key matters. IRWD is controlled by management and key top investors which, in our view, could be a positive or negative depending on the circumstances. Overall, we believe the most important feature of this structure is its ability to prevent a hostile takeover in the event IRWD's valuation becomes severely depressed. We view linaclotide as a primary care product with formidable long-term potential. However, we are also of the opinion the potential of linaclotide does not guarantee that IRWD will always be properly valued.

OUR THOUGHTS ON THE PHASE IIII IBS-C PROGRAM

The linaclotide Phase III program in IBS-C consists of two Phase III studies and an open-label safety study. Based on Phase II results, the only dose studied in the Phase III program is the 266 mcg/day. The CC Phase III program studied the 150 mcg and 300 mcg dose. (Due to the use of different measuring methods (peptides vs. linaclotide only), the 266mcg dose used in the Phase III contains the same amount of linaclotide as the 300mcg dose used in the Phase II programs.)

Study 31 is being administered by FRX and Study 306 by IRWD. For this reason, top-line reports will be made public at different times during Q4 2010.

Table 8: Linaclotide Pivotal Trials in IBS-C

Study 306	**n= ~800**	26 weeks on Linaclotide (266µg/day) or placebo	NA
Study 31	**n= ~800**	12 weeks on Linaclotide (266µg/day) or placebo	4 week randomized withdrawal phase

Source: IRWD reports, May 2010

Overall, the design of the pivotal program is compatible with recently published (March 2010) FDA draft guidance on the design of clinical trials in IBS-C. In fact, IRWD's consultants and scientists were active participants in the discussions leading to the publication of the draft guidance.

In our view, it is important to understand the background of the FDA's draft guidance for IBS drugs. The long-term goal of the FDA is to use patient reported outcome (PRO) instruments to evaluate IBS drugs. However, the development and validation of PRO instruments will take time to be incorporated in clinical trials (if ever, in our view). Therefore, the FDA March 2009 guidance serves as an interim recommendation on how to develop drugs for IBS.

Although key for the near-term profiling of the drug and IRWD's valuation, we believe the pain endpoint represents an imperfect (yet the best available) instrument to capture the benefits of a drug in an important symptomatic component of a complex syndrome (IBS). In fact, one could make the case that through additional studies, clinical experience and proper marketing, the long-term commercial prospects of the drug might not be significantly affected by any initial potentially negative pain data. However, we believe the near-term commercial prospects of the drug (and IRWD) are clearly affected by negative pain data (marketing message, formulary acceptance and pricing power).

The original statistical plan incorporates three co-primary endpoints (See Table 9) consisting of: **A:** patients responding to both pain and complete spontaneous bowel movement (CSBM) for 9/12 weeks; **B:** weekly improvements in stool frequency (CSBM) for 9/12 weeks; and **C:** weekly improvements in abdominal pain (a responder is defined as having a 30% average weekly reduction versus baseline pain score) for 9/12 weeks.

Study 306 goes for 36 weeks: Importantly, despite the measurement of primary endpoints at week 12, Study 306 continues for 26 weeks. In order for linaclotide to obtain a label for chronic treatment, we believe Study 306 needs to demonstrate linaclotide superiority over placebo throughout this period (The Zelnorm label only endorsed treatment for 12 weeks). Crucially, these results (differences) do not need to be statistically significant. So far, there has not been evidence of tachyphylaxis (decrease in the response) with linoclatide.

Additional endpoint: FRX and IRWD amended the trials' protocol to add an additional primary efficacy endpoint (which we call **endpoint D:** patients responding to both pain and complete spontaneous bowel movement (CSBM) for 6/12 weeks) which is more closely consistent with the FDA guidelines. We do not foresee any reason why the FDA will not accept the trials' change in protocol.

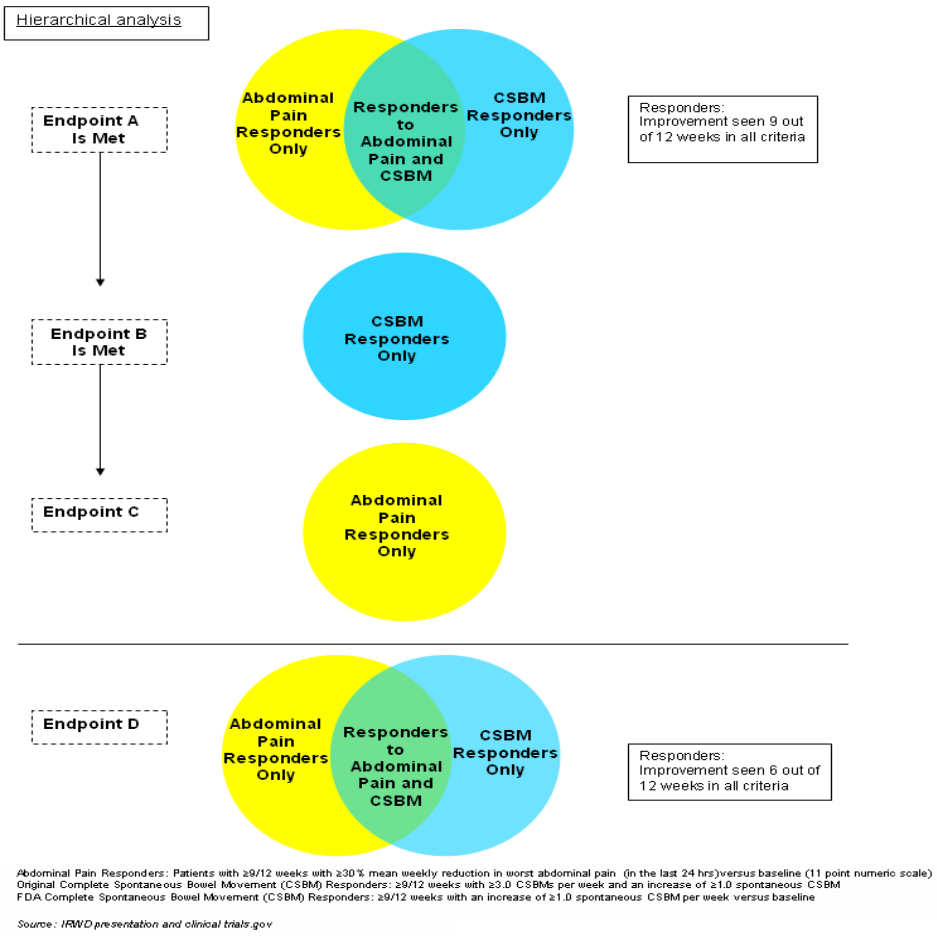
In essence, the new proposed endpoint (endpoint **D**) is similar to endpoint **A;** however, the definition of improvement in stool frequency is different (less stringent) and patients qualify as responders for 6/12 weeks (as opposed to 9/12 weeks) in the CSBM and pain endpoints.

Specifically, to qualify as a CSBM responder, endpoint D requires only an increase of one or more spontaneous CSBM per week versus baseline for 6/12 weeks (the original endpoint requires ≥9/12 weeks with ≥3.0 CSBMs per week and an increase of one or more spontaneous CSBM per week versus baseline).

In our view, in order for linaclotide to be granted a label including benefits in abdominal pain both trials need to meet endpoint A (patients responding to both endpoints) and more importantly endpoint C (the pain endpoint). Endpoint B (CSBM) supports an IBS-C indication but not a pain claim. Amitiza's IBS indication reads "for the treatment of IBS with constipation in women ≥18 years old"

Importantly, the statistical analysis of the results will be done in a hierarchical manner. As such, the first endpoint to be evaluated is endpoint A (patients responding two both endpoints). If this endpoint is met, the analysis moves to endpoint B (CSBM) and then (if endpoint B is met) to endpoint C (pain). The final endpoint in the sequence is endpoint D. The trials are powered >90% to demonstrate the superiority of linaclotide with a p-value of 0.05.

Hierarchy of Linaclotide's Endpoints (Pivotal Trials in IBS-C)



Our expectation is endpoint **A** will generate the lowest percentage of responders in both groups (placebo and linaclotide). However, we expect the relative therapeutic effect (delta of linaclotide versus placebo) to be strong and we believe the trial is well powered to show a statistically significant difference favoring linaclotide in this endpoint.

Consequently, we expect a higher percentage of responders in both groups (placebo and linaclotide) in the CSBM endpoint (B) and in the pain endpoint (C). We expect the pain endpoint to generate the highest percentage of responders; however, we expect the relative therapeutic effect will be similar throughout all endpoints. It is our bias endpoint A is somewhat the hardest endpoint to meet and once (if) it is met, the probability of meeting endpoints B and C remains very high.

In our view, endpoint **D** is significantly less stringent than endpoint **A**; therefore, one should expect the percentage of responders in both groups (placebo and linaclotide) to be higher than in endpoint **A**. However, we do not have a strong basis to argue endpoint **D** has a higher or lower chance of being met than endpoint A. In essence, we believe the probability of the trial to meet endpoint **D** is as good as the probability of it meeting endpoint A.

In our opinion, perhaps the most important benefit of the inclusion of endpoint D is for competitive reasons. Future drugs developed for IBS-C may choose the endpoints described in the FDA guidelines. If this is the case, other future drugs could be promoted against linaclotide with misguided higher response rates. The inclusion of results from endpoint **D** in scientific publications and potentially in the label would allow linaclotide marketers to strengthen the drug's position.

As discussed in the next section, we believe linaclotide's pivotal program has a high probability of generating a successful outcome that would warrant a label for the treatment of IBS-C including crucial label wording for abdominal pain.

Table 9. Linaclotide Phase III IBS-C Trial Primary and Secondary Endpoints

Primary Endpoints	A: CSBM + Pain Responder	B: CSBM Responder	C: Abdominal Pain Responder	D: Additional Endpoint
Linaclotide Phase III Definitions	≥9/12 weeks meets both the abdominal pain and CSBM responder criteria	≥9/12 weeks with ≥3.0 CSBMs per week and an increase of one or more spontaneous CSBM per week versus baseline	≥9/12 weeks with ≥30% mean weekly reduction in worst abdominal pain (in the last 24 hrs) versus baseline (11 point numeric scale)	50% of the time (6/12 weeks in this case): a) ≥30% mean weekly reduction in worst abdominal pain (in the last 24 hrs) versus baseline (11 point numeric scale); b) an increase of one or more CSBMs per week from baseline.
FDA Guideliness	NA	50% of the time (6/12 weeks in this case) with an increase of one or more spontaneous CSBM per week versus baseline	≥6/12 weeks with ≥30% mean weekly reduction in worst abdominal pain (in the last 24 hrs) versus baseline (11 point numeric scale)	50% of the time (6/12 weeks in this case): a) ≥30% mean weekly reduction in worst abdominal pain (in the last 24 hrs) versus baseline (11 point numeric scale); b) an increase of one or more CSBMs per week from baseline.
Secondary Endpoints				
CSBM (Complete Spontaneous Bowel Movement) Frequency SBM (Spontaneous Bowem Movement) Frequency Stool Consistency Severity of Straining Abdominal Pain Abdominal Pain-Free Days Abdominal Discomfort Adverse Events, ECGs, Vital Signs, and Clinical Labs				

* Scale asks patients to rate their worst abdominal pain over the last 24 hours. Weekly response is calculated by averaging the available daily pain assesments.

Source: IRWD presentation and clinicaltrials.gov (2010)

WILL LINACLOTIDE MEET THE ABDOMINAL PAIN ENDPOINT AND COMBINED ENDPOINT?

Clearly, whether linaclotide will meet the abdominal pain endpoint and the combined endpoint (pain+CSBM) are arguably the most important questions driving IRWD's near-term valuation. In our view, there are several factors that support the case for linaclotide generating positive abdominal pain results.

Linaclotide's mechanism of action provides an additional source of analgesia.

Linaclotide's analgesic effects in abdominal pain can result from: 1) improvements in bowel movements and 2) specific analgesic effect due to its unique mechanism of action.

1) The mechanical benefits of improving bowel movement is an effect shared with all other IBS-C therapeutic approaches. IBS-C is often defined as a disorder of abdominal discomfort and pain which improves with defecation. For this reason, improvement in CSMB and SBM often result in abdominal pain relief. However, the abdominal pain benefit seen with bowel movement improvements is mainly observed in situations of mild to moderate abdominal pain and the correlation between bowel symptom improvement and severe abdominal pain improvement is low.

For this reason, the pain benefit seen with linaclotide (more marked severe pain cases) could be also be explained by the physiological effects of its mechanism of action.

2) Specific activity of linaclotide on the guanylate cyclase type-C (GC-C) receptors results in increased cyclic GMP. Cyclic GMP plays a role in tuning down the hypersensitivity of the afferent nerve system which is believed to contribute to IBS symptoms.

In the context of human clinical trials, it is impossible to differentiate the analgesic benefit generated by mechanical improvements (defecation) versus cGMP effect. The strongest proof of linaclotide's (direct) effect on visceral pain was demonstrated in three different animal models and in multiple in-vitro analyses.

We believe the mechanical benefit (defecation) of linaclotide offers a certain level of analgesia which may not be strong enough to be clinically relevant and/or result in a positive Phase III result (30% reduction in pain for ≥9/12 weeks). As evidenced by analyses of the linaclotide Phase IIb IBS-C pain results, the correlation between pain response and stool frequency (CSBM) response is relatively poor.

In the linaclotide Phase IIb IBS-C clinical trial, the correlation between abdominal pain and CSBM frequency and SBM frequency was r=0.33 and r=0.13, respectively. The correlation between severe abdominal pain and bowel movement frequency was even weaker.

In the same trial, the correlation of abdominal pain/discomfort responders with constipation responders was "only fair" (r = 0.39).

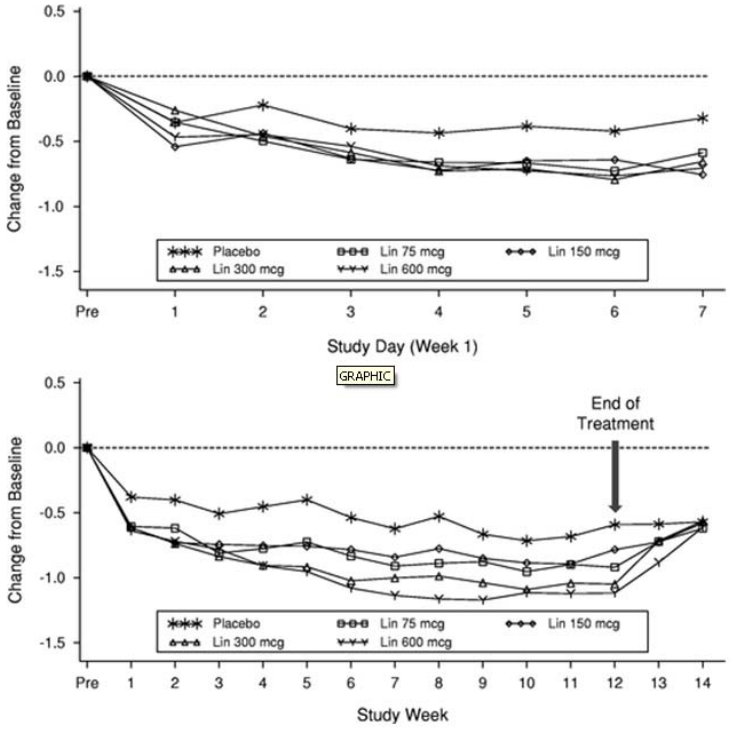
This "poor correlation" between a pain endpoint and a bowel (stool)endpoint has also been shown in non-constipation IBS studies. In the rifaximin Phase III trials in non-constipation IBS, the correlation between pain response and stool consistency response was also moderate to low.

In essence, we believe the analgesic benefit provided by linaclotide is independent from the stool frequency benefit seen with the drug and should be significant enough to generate a substantial number of responders under the trials' definition of pain response.

Existing analgesic results.

In the Phase IIb IBS-C study utilizing a 1-5 abdominal pain scale, linaclotide (at 300mcg) resulted in marked improvement in abdominal pain within the first week and the analgesic effect was sustained over the 12-week treatment period.

Table 10. Fast Onset (week 1) and Sustained Linaclotide Abdominal Pain Benefit



Source: IRWD S1, February 2010

Baseline pain values ranged from 2.87 to 3.13 (2.0 is considered mild and 3.0 is considered moderate). As seen on Table 11, abdominal pain was statistically significantly reduced in all linaclotide treatment groups compared to placebo. At the 300mcg dose, linoclatide patients had a -0.9 change from baseline vs. a -0.5 change for placebo. This represents a pain reduction of 46.8% versus baseline compared to a pain reduction of 25.6% versus baseline for placebo for the 300 mcg dose group (a 21.2% improvement relative to placebo).

The Phase IIb IBS-C study showed patients on linaclotide at 300 mcg also experience an increase of 18.5% in the median percentage of pain-free days (placebo was 2.0%). However, in the improvement

versus placebo at other doses (75 mcg, 150 mcg, and 600 mcg), numerical increases was observed but were not statistically significant.

Table 11. Linaclotide Phase IIb IBS-C Results in Abdominal Pain

Abdominal Pain	Placebo	75µg	150µg	300µg	600µg
N=	85	79	82	84	89
	-0.49	-0.71	-0.71	-0.9	-0.86
		p<0.05	p<0.05	p<0.001	p<0.001

Source: IRWD presentations, May 2010

Existing clinical results in the population with more severe abdominal pain.

Importantly, in the Phase IIb IBS-C trial, patients with severe pain at baseline experienced a greater pain benefit (however this analysis was based on small numbers as only 25% of enrolled patients met this severe pain criteria). Severe pain was defined as severe or very severe abdominal pain in ≥50% of the time during the pre-treatment period. In the Phase III IBS-C trial patients are enrolled in the trial if they have abdominal pain of ≥3.0.

Table 12. Linaclotide Phase IIb IBS-C Results in Severe Abdominal Pain

Severe Abdominal Pain	Placebo	75µg	150µg	300µg	600µg
N=	17	20	22	23	25
	-0.25	-0.83	-1.03	-1.21	-1.3
		p<0.05	p<0.001	p<0.001	p<0.001

Source: IRWD presentations, May 2010

Post-hoc analysis

IRWD performed a post-hoc analysis of the Phase IIb IBS-C study of the linaclotide 300 mcg/day dose utilizing the Phase III efficacy endpoints. Note in Table 13 that the treatment effect approximates 18% regardless of the endpoint (with 85 patients in the linaclotide arm and 84 patients in placebo). Additionally, we believe it is noteworthy relatively low placebo response rates were observed in a clinical trial where the probability of receiving an active drug was roughly 80%.

Importantly, we note the percentage of patients responding to the abdominal pain responder endpoint was significantly higher than the percentage of patients responding to the CSBM endpoint.

In essence, linaclotide is profiled as a drug primarily providing abdominal pain relief complemented by significant improvement in stool frequency. In our view, linaclotide is the only IBS drug with this therapeutic profile.

It is difficult to predict whether these figures will be similar in the ongoing Phase III trials. However, the fact that each Phase III trial enrolled approximately 800 patients (~400 per arm) gives us confidence the studies are well powered to demonstrate a difference between linaclotide and placebo. The linaclotide pivotal trials are 95% powered to demonstrate the expected differences on all endpoints.

Of note, we believe the addition of the fourth endpoint (endpoint D which mimics FDA guidelines) should result in a higher percentage of responders although we believe the chances for a positive outcome are unchanged.

Table 13. Linaclotide Phase IIb IBS-C Results Using FDA Guidelines for the Pivotal Trial

	Linaclotide 300µg	Placebo	Treatment Effect
	n=85	n=84	
A: Abdominal Pain and Complete Spontaneous Bowel Movement (CSBM) Responder Analysis	27%	10%	17%
B: CSBM Responder Analysis	31%	13%	18%
C: Abdominal Pain Responder Analysis	48%	30%	18%

Source: IRWD reports, May 2010

Frequency of testing.

The trial requires patients to telephonically rate their worst abdominal pain over the last 24 hours on a daily basis. Then, a weekly response (≥30% improvement) is calculated based on the mean improvement in pain during the week (we estimate a minimum of 4 days). Lastly, a patient is considered a responder if there is a ≥30% improvement in pain in 9/12 weeks (original endpoint) or 6/12 weeks (FDA guidelines and new co-primary endpoint).

In our view, the frequency of testing (daily) increases the power of the trial to capture analgesic benefit as it removes some of the variability associated with pain recollection over longer periods of time (e.g. a week).

The use of a 11 point numeric scale.

Importantly, the Phase III IBS-C trial uses an 11 point pain scale (0 to 10) as opposed to the 1-5 pain scale used in earlier linaclotide trials. 11 point pain numeric scales are the norm in most chronic pain clinical studies and are preferred by the scientific community and the FDA Division of Anesthesia, Analgesia and Rheumatology products. In essence, we see the use of a 1-5 pain scale (or 1-6 or 1-7 scales used in other IBS trials) as an anomaly highlighting the lack of consensus (or sophistication) in evaluating abdominal pain by the gastro-intestinal community.

In essence, the 11 point pain scale is somewhat more sensitive than a 5 point (1 to 5) pain scale which we view as a positive. However, we believe there could be a potential small “drawback” in dealing with moderate pain. For example, when a given patient with moderate pain (3 at baseline) experiences a modest pain reduction, the patient can easily rate pain during treatment as a 2 (a 30% benefit) since 2 is the only option that still allows the patient to document improvement.

However, on an 11 point pain scale, the same patient could manifest a baseline pain of 5 or 6 and modest improvements could be given a 1 point benefit (as opposed to the 2 points required to demonstrate a 30% pain reduction as the responder analysis indicates).

Since this potential small “drawback” affects both arms (placebo and the treating arm), we do not believe it is detrimental to use an 11 point pain scale. Rather, overall response rates could be lowered in both groups (compared to using the 5 point scale) and there may be a slight improvement in the probability of a successful outcome since the percentage of placebo responders may decrease more. We believe the trial is adequately powered to incorporate these variables.

Asking for the worst abdominal pain.

The 11 point pain scale specifically asks patients to rate the worst abdominal pain they experienced over the last 24 hours. In our view, this is different than rating pain (abdominal) intensity over the last 24 hours or the last week as is routinely asked in chronic pain trials. Most patients with chronic pain (not IBS related or visceral) have daily fluctuations in pain intensity. However, pain is the primary complaint of these patients and there is always a certain degree of background pain. For this reason, scales focusing on pain intensity changes (and not worst pain) are adequate.

Although abdominal pain is a key component of IBS, it is not always a patient's primary daily complaint. Additionally, the intensity of abdominal pain could fluctuate throughout the day and often comes in waves, some of which may be very intense. For this reason, by focusing on the worst abdominal pain, the questionnaire mainly evaluates the alleviation of severe pain episodes (where linaclotide has differentiated from placebo and has demonstrated the strongest analgesic effect).

Chronic abdominal (visceral pain) has not been widely studied.

We believe it is also important to consider the chance of success for any chronic pain trial. Chronic visceral pain has not been as widely studied as chronic neuropathic pain. However, there is a plethora of clinical trials in chronic neuropathic pain with negative outcomes even when molecules are known to be effective. For this reason, investors should not underestimate the inherent risk of evaluating chronic pain in any clinical trial.

In addition, many patients with IBS-C complain of pain (and other symptoms) intermittently. For example, a patient's primary concern may be pain 2 days out of a week and have bloating or other discomforts. However in the Phase III linaclotide IBS-C trial, the baseline pain score is established over a two week pre-treatment period. During this period, we believe there are enough days where pain will be the #1 complaint with several episodes of pain during the other days to obtain a reliable baseline pain score reading and meet the trials' entry criteria.

WILL LINACLOTIDE MEET THE BOWEL MOVEMENT (CSBM) ENDPOINT?

Based on available Phase IIb results in IBS-C and Phase III results in CC we are confident in our opinion linaclotide's pivotal program will likely meet the CSBM responder endpoint. We are also confident the majority of the secondary endpoints will render positive results as well.

The primary endpoint in the Phase IIb IBS-C trial was the change in CSBM weekly frequency. The mean baseline CSBM frequency was 0.29 a week (68% of patients had no CSBM at all). Patients receiving linaclotide at 300mcg experienced a mean improvement in CSBM frequency of 3.61 vs. a mean improvement of 1.01 in the placebo group ($p<0.001$).

Table 14. Linaclotide Phase IIb IBS-C CSBM Weekly Frequency Results

	Placebo	75µg	150µg	300µg	600µg
N=	85	79	82	84	89
Baseline: 0.29					
Change in the overall week frequency of CSBMs (number/week)	1.01	2.9	2.49	3.61	2.68
		p<0.001	p<0.01	p<0.001	p<0.001

Source: IRWD presentations, May 2010

In the Phase III trial, a CBMS responder is defined as a patient who has at least 3 CSBMs per week (in 9 out of 12 weeks) and an improvement in CSBM frequency of at least 1.0 over baseline.

In our view, baseline characteristics (we expect baseline CSBM frequency to be similar to those seen in the Phase IIb trial) and results from the Phase IIb IBS-C trial suggest a ≥1.0 improvement in CBMS frequency and ≥ 3.0 CSBMs a week are attainable targets.

If the results are analyzed applying FDA guidelines (the basis for endpoint D), we expect the percentage of patients with an improvement in CSBM frequency of at least 1.0 over baseline in ≥6/12 weeks to be significantly higher.

Can linaclotide's effect be maintained for 9/12 weeks? Phase IIb data shows linaclotide improved multiple IBS-C symptoms in the first week of treatment and such improvements were maintained throughout the 12 weeks of the study. Table 15 below describes the magnitude of the response within the first week of treatment. Similar results were seen in the Phase III CC results.

Table 15. Week 1: Changes from Baseline in IBS-C Symptoms

Week 1: Mean Change from Baseline	Placebo	75µg	150µg	300µg	600µg
Abdominal Discomfort (1-5 scale)	-0.33	-0.52	-0.49	-0.63	-0.6
		p=0.03	p=0.0693	p=0.0006	p=0.0019
Bloating (1-5 point point scale)	-0.26	-0.54	-0.48	-0.6	-0.56
		p=0.0039	p=0.0222	p=0.0004	p=0.0016
Stool Consistency (1-7 point scale)	0.39	1.76	1.9	1.96	1.96
		p<0.0001	p<0.0001	p<0.0001	p<0.0001
Straining (1-5 point scale)	-0.52	-1.09	-1.17	-1.3	-1.21
		p<0.0001	p<0.0001	p<0.0001	p<0.0001
Global Relief (1-7 point scale)	0.62	-1.23	-1.16	-1.29	-1.41
		p<0.0001	p=0.0003	p<0.0001	p<0.0001
Adequate Relief Responders (Yes/No)*	29%	51%	51%	68%	63%
		p<0.01	p<0.01	p<0.001	p<0.001

Source: IRWD presentations, May 2010

Phase III Results in CC. Although the FDA sees chronic constipation (CC) and IBS-C as two different indications for regulatory purposes, IRWD and many experts believe the symptoms underlying both conditions can be viewed as a continuum with a varying degrees of bowel habit or constipation symptoms (stool consistency, CBMS, straining) and abdominal symptoms (pain, discomfort, bloating).

For this reason, it is important to incorporate linaclotide's effects on bowel motility in the CC trial. In addition, the primary endpoint in the Phase III CC trial was a CSBM responder analysis, which is the same endpoint used in the IBS-C pivotal trials (≥1.0 improvement per week in CBMS and ≥3.0 per week in 9/12 weeks).

Both CC trials (Trial 01 and Trial 301) met the primary endpoint at both doses (133mcg and 266mcg). In addition, all 32 secondary endpoints, including CSBM frequency, SBM frequency, stool consistency, severity of straining, bloating, abdominal discomfort and constipation severity, were met in both dose groups with strong p-values.

Study 303 included a 4-week randomized withdrawal period following the 12-week treatment period. Patients who were on linaclotide and randomized to placebo quickly lost benefit (to levels similar to placebo). On the other hand, placebo patients randomized to linaclotide quickly gained benefit.

Table 16. Chronic Constipation Phase III Results

Trial 01: 12 weeks	Placebo	133µg	266µg
N= 630	215	213	202
Baseline CSBM: 0.3			
CSBM responder at 12 weeks	13 (6%)	34 (16%)	43 (21.3%)
		p=0.0012	p<0.0001
CSBM rate change ≥1.0	55 (25.6%)	105 (49.3%)	115 (56.9%)
		p<0.0001	p<0.0001

Trial 303: 12 weeks + 4 week randomized withdrawal			
N= 642			
Baseline CSBM: 0.3			
	Placebo	133µg	266µg
CSBM responder at 12 weeks	3.30%	21.20%	19.40%
		p<0.0001	p<0.0001
CSBM rate change ≥1.0 for 9/12 weeks	11%	39.20%	37%
		p<0.0001	p<0.0001
CSBM rate ≥3.0 for 9/12 weeks	3.80%	21.70%	19%
		p<0.0001	p<0.0001

Source: DDW 2010

Consistency across endpoints. Linaclotide demonstrated positive results in several secondary endpoints in the Phase IIb IBS-C trials. In addition, linaclotide met all 32 endpoints in the Phase III trials in CC. In our view, this level of consistency in the results increases our confidence (and in our opinion, the confidence of regulators) of the clinical benefits of linaclotide.

Table 17. IBS-C Phase IIb Results

Endpoint	Placebo	75µg	150µg	300µg	600µg
% change from baseline					
Abdominal pain (% change from baseline)	25.6%	37.1%	36.9%	46.8%	44.4%
Abdominal discomfort (% change from baseline)	22.1%	31.3%	32.5%	42.7%	38.6%
Bloating (% change from baseline)	16.1%	27.3%	25.5%	37.3%	31.6%
IBS severity (% change from baseline)	22.2%	35.0%	34.1%	42.1%	41.0%
Constipation severity (% change from baseline)	23.3%	42.3%	41.1%	53.8%	48.8%
≥0.5 point improvement (approximations from charts in corporate presentation)					
Abdominal pain (≥0.5 point improvement)	37.0%	57.0%	53.0%	59.0%	60.5%
Abdominal discomfort (≥0.5 point improvement)	32.0%	52.0%	54.0%	60.0%	63.0%
Bloating (≥0.5 point improvement)	24.0%	54.0%	50.0%	59.0%	55.0%
% Patients with adequate relief	29%	51%	51%	68%	63%

Source: IRWD presentations, May 2010

Table 18. Chronic Constipation Phase III Endpoints

	Trial 303		Trial 01	
	133 mcg	266 mcg	133 mcg	266 mcg
Weekly CSBM Rate	p<0.0001	p<0.0001	p<0.0001	p<0.0001
Weekly SBM Rate	p<0.0001	p<0.0001	p<0.0001	p<0.0001
Stool Consistency	p<0.0001	p<0.0001	p<0.0001	p<0.0001
Severity of Straining	p<0.0001	p<0.0001	p<0.0001	p<0.0001
Overall Constipation Severity	p<0.0001	p<0.0001	p<0.0001	p<0.0001
Overall Abdominal Discomfort	p=0.0003	p=0.0063	p=0.0006	p=0.0001
Overall Bloating	p<0.0001	p=0.0049	p=0.0005	p<0.0001
Overal PAC-QOL	p<0.0001	p<0.0001	p<0.0001	p<0.0001

Source: IRWD Reports (S1), February 2010

LINACLOTIDE HAS A CLEAN SAFETY PROFILE

In our view, the favorable safety profile of linaclotide reported to date represents one of the strongest differentiating characteristics of the drug. For this reason, if approved, we believe linaclotide should be widely used by all physicians (including PCPs) and therefore should become a blockbuster.

Linaclotide's main side effect is mild diarrhea (consistent with the drug's mechanism) at the chosen doses for the pivotal trials. We believe the 133mcg (150mcg) dose is appropriate to offer satisfactory bowel benefits. However, we believe the 266mcg (300mcg) dose properly addresses abdominal symptoms and the higher dose (600mcg) did not show significant additional benefit.

Linaclotide is not absorbed and the duration of its therapeutic effect is limited by the average renewal of the luminal aspect of intestinal epithelium (approximately 3 days). In fact, clinical trials have shown the efficacy of the drug quickly wanes down after therapy interruption. If a patient develops diarrhea, therapy interruption has been seen to offer rapid relief.

Table 19. Adverse Effects Phase II IBS-C Trial

	Placebo	75µg	150µg	300µg	600µg
Adverse Effects					
Diarrhea	1 (1%)	9 (11%)	10 (12%)	14 (16%)	16 (18%)
Severe diarrhea	0	2 (3%)	2 (2%)	1 (1%)	4 (5%)
Discontinuation due to diarrhea	0	2 (3%)	4 (5%)	1 (1%)	6 (7%)

Source: IRWD presentations

Table 20. Adverse Effects Phase III CC Trials

	Placebo	133µg	266µg
Adverse Events (Combined)			
Diarrhea	20 (5%)	69 (16%)	60 (14%)
Flatulence	22 (4%)	24 (6%)	21 (5%)
Discontinuation due to diarrhea	2 (0.5%)	19 (4%)	16 (4%)

Source: DDW 2010

PROBABILITY OF MEETING ENDPOINTS

To obtain a label claim for abdominal pain, we believe the pivotal trials need to generate positive outcomes in the abdominal pain endpoint (as well as the composite endpoint or endpoint A).

However, we acknowledge that in the case where only one trial meets the abdominal pain endpoint or the composite endpoint, the chance of linaclotide obtaining a label claim for abdominal pain will become a source of investor debate.

We also believe there could be different ways for linaclotide to obtain a label that includes support for abdominal pain benefit (e.g. strong secondary endpoint support, mixed trials, a positive pooled analysis). A simplistic view of potential positive outcomes can be summarized as follows:

We assign a 90% probability to a given trial meeting the pain+CSBM endpoint and a 95% probability for a given trial meeting both the CSBM and the abdominal pain endpoints.

Alongside, we assign a 95% probability to a given trial meeting the combined endpoint D (pain + CSBM).

Additionally, according to these assumptions, the chance of both linaclotide Phase III IBS-C studies meeting all three original primary endpoints is 66% [(90% x 90%)*(95% x 95%)*(95% x 95%)].

However, the probability of a successful outcome could be higher and reach 74% if we incorporate endpoint D (in the event the trials miss endpoint A) [(90% x 90%)*(95% x 95%)*(95% x 95%)].

Table 21. Probability of Meeting Endpoints

	Chance of Occurrence	Label Claim	Linaclotide North American Revenues	Linaclotide P&L Profit Estimate for IRWD (North America)(appx. 2016) ($000s)	Valuation Estimate (Price ($) per share)
A. Pain+CSBM Responder Analysis (both trials)	81%	CC and/or IBS (no pain)	514,851	163,289	4.99
B. CSBM Responder Analysis (both trials)	90%	CC and/or IBS (no pain)			
C. Abdominal Pain Responder Analysis (both trials)	90%	CC+IBS (including pain)	1,284,256	477,996	18.64
Combined	**66%**	**CSBM+Pain**	**1,284,256**		**13.61**
Non Approval	5%	CC	250,000	NA	3.20

Source: Ladenburg Thalmann & Co. estimates

CONSEQUENCES OF A FAILING TRIAL

We believe existing data warrants approval for CC. In our view, if the composite endpoint and/or CSBM are the only co-primary endpoints met in the trials, we believe linaclotide is approvable for IBS-C (improvement in bowel habits only) with a label claim excluding abdominal pain benefit.

Under this scenario (downside case), we estimate linaclotide could lose pricing power, payers would be slower to endorse the drug, and the initial marketing message would be weaker and could potentially result in a slow initial uptake of the drug.

However, long-term we believe there is a strong case for linaclotide reaching a significant revenue mark even in the absence of a pain claim in the label. In our opinion, investors should bear in mind safety (when combined with an acceptable degree of efficacy) is a primary factor in wide adoption (especially among primary care physicians).

In addition, we believe the failure to meet the pain endpoint in the pivotal trials could be the result of peculiarities intrinsic to clinical trials (design, assumptions, placebo effect, chance, etc.) and not a definitive statement against the drug's effects on abdominal pain. For this reason, in the context of limited competition, we believe linaclotide's safety and efficacy profile, as well as clinician experience with the drug, could allow FRX and IRWD to design marketing strategies (and post-marketing studies) to turn linaclotide into a blockbuster drug in the long-term.

However, we acknowledge that if linaclotide fails the pain endpoint there will be a degree of skepticism (by the Street) about the commercial prospects of the drug. Consequently, our worst case scenario assumes linaclotide has no effect on abdominal pain. Under this scenario, we estimate linaclotide's US revenue potential to be $435 million.

Under this scenario, our model predicts linaclotide's P&L to become cash flow positive once revenues of approximately $200 million are reached. For this reason, in this downside case, IRWD's share of profits would be relatively modest ($160 to $170 million) setting a $5.00 valuation level.

WHAT ABOUT EUROPE?

The EMA agreed Almirall can use the US Phase III IBS-C trials as the basis for a market authorization application. However, the endpoints are different. In Europe, the co-primary efficacy endpoints are: 1) abdominal pain/abdominal discomfort and 2) IBS degree of relief.

1) Abdominal pain/abdominal discomfort endpoint: Defined as a patient who, for ≥6 /12 weeks of the treatment period, has an improvement from baseline of 30% or more in either the mean abdominal pain score or mean abdominal discomfort score for that week with neither of these scores worsening from baseline for that week. The endpoint is measured daily using a 1-10 scale.

2) IBS degree of relief endpoint: Defined as a patient whose response to the degree of relief of IBS symptoms question is "Considerably Relieved" or "Completely Relieved" (i.e., a score of ≤ 2 on a 7 point scale) for ≥6 /12 weeks.

In essence, the European endpoints incorporate significant improvements from endpoints used in prior IBS clinical trials, but do not fully incorporate suggestions set forth by the FDA in the FDA's new draft guidance. We believe the European results could potentially clearly describe how (and which) patients are benefiting from treatment with linaclotide (The US trial results are defined by the limitations of stringent definitions off responders and composite analyses).

Utilizing the abdominal pain/abdominal discomfort and the IBS degree of relief endpoints, we expect the percentage of patients likely to meet the responder criteria in European trial analyses will be higher than in the US analyses. In addition, the European trial does not have a composite endpoint as a primary endpoint. We believe the European trial results more closely describe how patients are benefiting from treatment with linaclotide (the results from the US are limited by the statistical analysis of complicated endpoint criteria). Consequently, we assign a higher probability of success to the European trials' analyses.

Table 22. Primary efficacy endpoints used in IBS trials

Product	Indication	Primary Endpoint	Questions Used to Assess Endpoint	Response
Alosetron	IBS-D	Adequate relief	In the past 7 days, have you had adequate relief of your IBS pain or discomfort?	Binary endpoint (Yes/No)
Tegaserod	IBS-C	Satisfactory relief	Over the past week, do you consider that you have had satisfactory relief from your symptoms of IBS?	Binary endpoint (Yes/No)
			Did you have satisfactory relief of of your overall IBS symptoms during the last week?	Binary endpoint (Yes/No)
			Did you have satisfactory relief of your abdominal discomfort or pain during the last week?	Binary endpoint (Yes/No)
		Subject Global Assessment of Relief	Please consider how you felt during the past treatment period in regard to your IBS, in particular your overall well-being, and symptoms of abdominal pain/discomfort and altered bowel habit.	5-Point Likert scale: worse, not at all relieved, somewhat relieved, considerably relieved, completely relieved
Lubiprostone	IBS-C	Subject Global Assessment of Relief (modified version)	How would you rate your relief of IBS symptoms (abdominal discomfort/pain, bowel habits, and other IBS symptoms) over the past week compared with how you felt before you entered the study?	7-Point Likert scale: substantially worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, substantially improved

Source: Guidance for Industry: Irritable Bowel Syndrome --- Clinical Evaluation of Products for Treatment (draft guidance), US DHHS, FDA and CDER, March 2010

COMMERCIAL CONSIDERATIONS

Epidemiological studies report US prevalence figures of 11-13 million for IBS-C and approximately 33 million for CC.

Generally speaking, patients with frequent and/or severe symptoms poorly controlled by over the counter (OTC) products are likely to consult physicians. IRWD estimates (based on several published studies) between 9 million to 15.5 million IBS-C and CC patients seek medical care.

Unfortunately, patients taking prescription or OTC laxatives continue to experience poor outcomes with approximately 70% of IBS-C patients reporting unsatisfactory treatment results to prescription medicines (as measured by therapy interruption after 60 days of initiation) . This figure is thought to be similar in CC patients. As a reminder, 68% of patients enrolled in the linaclotide CC study had no CSBM at baseline.

Importantly, patient surveys have shown that the most severe patient population continues to seek medical care (in search for better solutions) rather frequently despite poor past experiences. In our view, having an active patient population already engaged with the treating physician provides an easier market to penetrate in the early stages of launch.

In our view, the market for linaclotide represents the patient population with abdominal symptoms (pain, bloating and discomfort) that has not responded well to OTC or prescription laxatives, stool softeners, fiber products, et cetera.

Since these symptoms (pain, bloating and discomfort) are more predominant in IBS-C patients, we expect this market to be the primary focus for linaclotide and the one that provides the best pricing alternatives. In fact, the CC market has been a difficult market to penetrate by novel prescription medicines as they offer minimal additional benefit over OTC options.

PEG (Polyethylene glycol; marketed as Miralax, available OTC and by prescription) and lactulose (prescription only) are the predominant laxatives used to treat IBS-C and CC. These approaches have proven relatively effective at treating bowel symptoms (alleviating constipation) but lack significant effect on pain, bloating and global IBS symptoms (in fact, some patients experience exacerbation of cramping and diarrhea). A recently published Cochrane meta-analysis (in CC only) concluded PEG is better than lactulose in outcomes of stool frequency per week, form of stool, and the need for additional products in adults (effects in pain were comparable in adults).

Other laxatives such as disacodyl (Dulcolax) have been studied in IBS-C and have very limited utility for chronic usage. Stool softeners (e.g. Colace) are rarely helpful in the treatment of IBS-C.

As seen on Table 23, the American College of Gastroenterology task force assigns grades of supporting evidence (risk/benefit and quality of evidence) to laxative and fibers. We also believe the credit given to Amitiza and triclyclics at treating pain should be significantly reduced when applying current FDA guidelines (which could potentially happen in future ACG updates)

Table 23. Evidence-Based Summary of IBS-C Therapies

	Global IBS Symptoms	Pain	Bloating	Stool Frequency	Stool Consistency	Grade
Fiber				+	+	2C
Laxatives (polyethylene glycol)				+		2C
Amitiza	+	+			+	1B
Tricyclic Antidepressants	+	+				1B
Zelnorm	+	±	+	+	+	2A

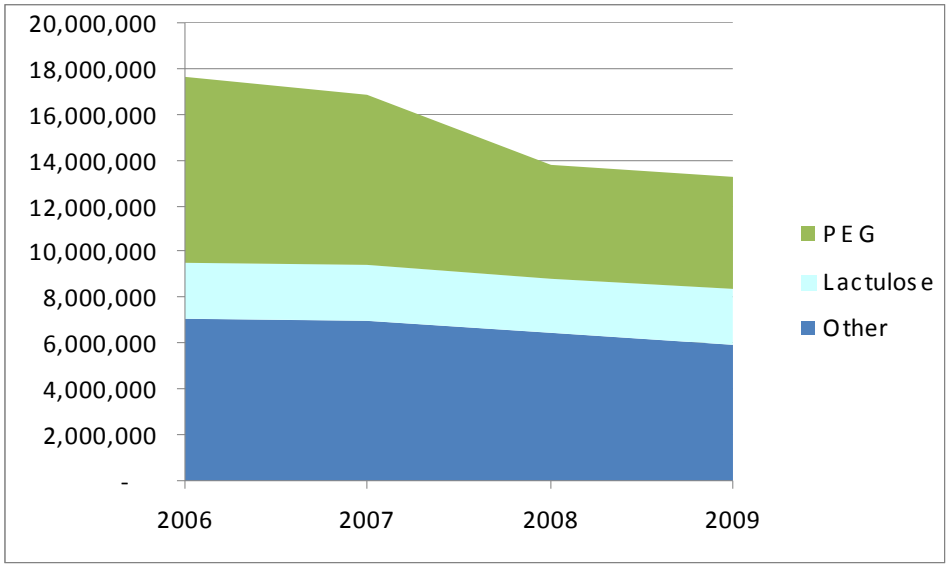
Risk/Benefit, Burden and Cost: Grade1: strong / Grade 2: weak

Quality of evidence (study design, quality of endpoints, consistency among trials): A:high / B:moderate / C:low

Source: ACG task force on IBS; American Journal Gastroenterogy 2009; 1049 (Suppl 1)

Nevertheless, prescriptions of PEG products approximated 7 million prescriptions a year in 2006. Miralax became an OTC product in early 2007 (current PEG prescriptions approximate 5 million a year). Lactulose prescription approximate 2.4 million per year. Total prescriptions of laxatives reached 17 million in 2006 (currently at 13 million a year).

Table 24. Laxative Prescriptions



Source: Wolters Kluwers PHAST

Zelnorm: Zelnorm, approved in 2002, was the first drug to offer satisfactory relief of IBS symptoms as well as benefits (although very modestly) in abdominal pain and bloating. Despite not fully addressing pain and bloating, Zelnorm reached US peak revenues of $488 million ($561 million worldwide representing 34% YoY growth) five years after its launch. Zelnorm was withdrawn from the market in 2007 due to safety and increased risk of cardiovascular events.

We believe linaclotide's safety and efficacy profile are unprecedented in the space and should dramatically transform the IBS-C market. Linaclotide is not absorbed systemically, lacks cardiovascular risks, only needs to be taken once-a-day and has pronounced effects on bowel habits, abdominal pain and bloating.

Table 25 describes linaclotide's mean improvement versus baseline in key symptomatic figures as well as the percentage of patients reaching clinically relevant responses. In our view, this level of response is rare in therapies offering symptomatic benefit and could be partially compared (in the world of gastroenterology) to symptomatic responses seen with the use of proton pump inhibitors (PPI) in the treatment of GERD.

Table 25. Linaclotide Offers Strong Improvements in Multiple Domains of IBS-C

Endpoint	Placebo	75µg	150µg	300µg	600µg
% change from baseline					
Abdominal pain (% change from baseline)	25.6%	37.1%	36.9%	46.8%	44.4%
Abdominal discomfort (% change from baseline)	22.1%	31.3%	32.5%	42.7%	38.6%
Bloating (% change from baseline)	16.1%	27.3%	25.5%	37.3%	31.6%
IBS severity (% change from baseline)	22.2%	35.0%	34.1%	42.1%	41.0%
Constipation severity (% change from baseline)	23.3%	42.3%	41.1%	53.8%	48.8%
≥0.5 point improvement (approximations from charts in corporate presentation)					
Abdominal pain (≥0.5 point improvement)	37.0%	57.0%	53.0%	59.0%	60.5%
Abdominal discomfort (≥0.5 point improvement)	32.0%	52.0%	54.0%	60.0%	63.0%
Bloating (≥0.5 point improvement)	24.0%	54.0%	50.0%	59.0%	55.0%
% Patients with adequate relief	29%	51%	51%	68%	63%

Source: IRWD presentations, May 2010

Similar to GERD Therapies? Sustained resolution of heartburn after 28 days (in patients with erosive esophagitis) reaches rates of 68% to 74% for omeprazole and esomeprazole. Proton pump inhibitor (PPI) high response rates have resulted, over the years, in high patient compliance (>220 days) and significant market penetration (19 million patients (42%) out of 45 million Americans suffering from GERD receive prescription medicines). However, multiple drugs in this class were necessary to get to these levels of market penetration.

We are not arguing linaclotide will result in similar compliance rates or market penetration. However, we believe the PPI market represents a proxy (a distant or not too distant proxy depending on individual perspective) for the way we believe the market for symptomatic treatment of abdominal visceral pain, bloating and abdominal discomfort (including IBS) can evolve over time. IRWD estimates 17% (~2 million) of the 12 million patients with IBS-C currently receive prescription medicines.

Linaclotide Revenue Model

We believe linaclotide has the potential to be used by approximately 1.0 million IBS-C patients and 240,000 CC patients (at peak).These figures represent a market penetration of 6.6% and 1.0%, respectively. In addition, we expect significant off label use (~250,000 patients) in patients where symptoms of abdominal pain, discomfort and bloating are prevalent (gastropareisis, dyspepsia, etc).

As such we believe linaclotide has the potential to generate revenues of >$1.3 billion in the U.S. after five to six years on the market. We expect the compliance rate to approximate 190 days in patients with IBS-C and 50 days in CC patients. We project linaclotide revenues to reach approximately $120 million in CC alone. At present, we do not believe there is enough evidence that CC represents a large market (relative to IBS-C) for a novel prescription medicine.

We estimate approximately 900,000 IBS-C patients will receive treatment at peak, representing an IBS-C market penetration of 6%. We believe linaclotide will be adequately priced for a drug that is expected to be widely prescribed (starting ~$5.5 a day in our model). Recall we expect linaclotide's safety profile to allow the commercialization of the drug into multiple medical specialties, including the large primary care market.

Table 26. Linaclotide US Revenue Model ($000s)

US Irritable Bowel Syndrome-C	2011E	2012E	2013E	2014E	2015E	2016E	2017E	2018E
Prevalence of IBS	12,400	12,710	13,028	13,353	13,687	14,029	14,380	14,740
Patients Self Medicated	8,680	8,897	8,859	8,680	8,897	9,119	9,203	9,433
Self Medicated	70%	70%	68%	65%	65%	65%	64%	64%
Patients Seeking Care	3,720	3,813	4,169	4,674	4,791	4,910	5,177	5,306
Seeking Care	30%	30%	32%	35%	35%	35%	36%	36%
Patients Receiving Pharmacological (Rx) Treatment	2,000	2,050	2,101	2,154	2,208	2,263	2,319	2,377
Patients Receiving Novel Pharmacological (Rx)* Treatment	150	170	250	374	527	737	999	1,114
	4%	*4%*	*6%*	*8%*	*11%*	*15%*	*19%*	*21%*
Linaclotide Penetration	0	14	125	262	422	626	849	947
	0%	*8%*	*50%*	*70%*	*80%*	*85%*	*85%*	*85%*
Cost per Day	$5.5	$5.5	$5.7	$5.9	$6.2	$6.4	$6.7	$6.9
Compliance (Days)	200	200	200	190	190	190	190	190
Revenue per Patient	$1,100	$1,100	$1,144	$1,130	$1,175	$1,223	$1,271	$1,310
Total US IBS-C Revenues	**$0**	**$14,960**	**$143,076**	**$295,823**	**$495,546**	**$765,366**	**$1,079,758**	**$1,240,365**
US Chronic Constipation	**2011E**	**2012E**	**2013E**	**2014E**	**2015E**	**2016E**	**2017E**	**2018E**
Prevalence of CC	34,000	34,850	35,721	36,614	37,530	38,468	39,430	40,415
Patients Receiving Novel Pharmacological (Rx)* Treatment	150	180	250	330	826	1,000	1,104	1,132
	4%	*5%*	*7%*	*9%*	*11%*	*13%*	*14%*	*14%*
Linaclotide Penetration	0	2	13	40	165	230	331	339
	0%	*1%*	*5%*	*12%*	*20%*	*23%*	*30%*	*30%*
Cost per Day	$5.5	$5.5	$5.7	$5.9	$6.2	$6.4	$6.7	$6.9
Compliance (Days)		45	45	50	50	50	50	50
Revenue per Patient	$0	$248	$257	$297	$309	$322	$335	$345
Total US CC Revenues	**$0**	**$446**	**$3,218**	**$11,762**	**$51,081**	**$74,006**	**$110,816**	**$116,994**
Off-Label Use (Dyspepsia, Gastropareisis, etc)								
Linaclotide Penetration			4	18	40	120	200	200
Cost per Day	$5.5	$5.5	$5.7	$5.9	$6.2	$6.4	$6.7	$6.9
Compliance (Days)		70	70	70	70	70	70	70
Revenue per Patient	$0	$385	$400	$416	$433	$450	$468	$482
Total US Off-Label Revenues	**$0**	**$0**	**$1,602**	**$7,495**	**$17,323**	**$54,047**	**$93,682**	**$96,493**
TOTAl US Linaclotide Revenues	**$0**	**$15,406**	**$147,896**	**$315,081**	**$563,950**	**$893,419**	**$1,284,256**	**$1,453,852**

* Amitiza and linaclotide only, exludes PEG and other laxatives

Source: Ladenburg Thalmann estimates

European estimates:

In our view, the IBS market in Europe is immature in comparison to the US. No drug has been approved in Europe for the treatment of IBS. In our opinion, linaclotide has the potential to be transformative to Almirall, a mid-size European (Spanish based) company lacking pan European reach. We believe these dynamics offer great opportunities but also come with significant levels of uncertainty.

Our model assumes linaclotide could generate peak revenues of $240 million in Europe. At this point, we have a moderate valuation for linaclotide's opportunity outside of the U.S.

Table 27. Linaclotide European Revenue Estimates

EUROPE Irritable Bowel Syndrome-C	2011E	2012E	2013E	2014E	2015E	2016E	2017E	2018E
Prevalence of IBS	14,000	14,350	14,709	15,076	15,453	15,840	16,236	16,642
Patients Receiving Pharmacological (Rx) Treatment	840	1,148	1,471	2,111	2,627	2,851	3,085	3,328
	6%	*8%*	*10%*	*14%*	*17%*	*18%*	*19%*	*20%*
Patients Not Optimally Treated	588	804	1,103	1,583	1,970	2,195	2,375	2,563
	70%	*70%*	*75%*	*75%*	*75%*	*77%*	*77%*	*77%*
Linaclotide Penetration	0	0	11	40	118	220	238	256
	0%		*1%*	*3%*	*6%*	*10%*	*10%*	*10%*
Cost per Day	$4.5	$4.7	$5.0	$5.2	$5.5	$5.7	$6.0	$6.3
Compliance (Days)	150	155	155	155	160	165	165	166
Revenue per Patient	$675	$732	$769	$807	$875	$948	$995	$1,051
TotalEurope IBS-C Revenues	**$0**	**$0**	**$8,483**	**$31,955**	**$103,461**	**$208,043**	**$236,346**	**$269,378**
Royalties to IRWD			**1,697**	**7,989**	**25,865**	**52,011**	**59,086**	**67,344**

Source: Ladenburg Thalmann estimates

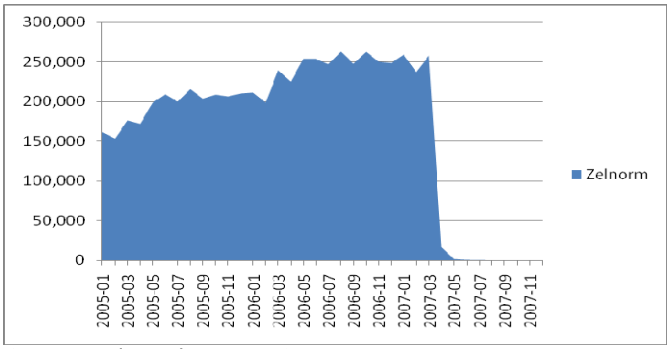
Prescription-Based Estimates

Given potential inaccuracies in prevalence studies, including variability on symptom severity and frequency, as well as variability in treatment compliance and the use of prescription and OTC medication usage, we believe it would not be completely adequate to use these figures as the sole input to estimate the potential market for linaclotide.

In order to estimate the market potential for linaclotide, we believe one has to complement prevalence studies with the historical level of prescriptions reached by Zelnorm, Amitiza and PEG products, as well as other laxatives.

Zelnorm, Again. At peak Zelnorm averaged roughly 250,000 prescriptions a month and reported roughly 3 million prescriptions in the 12 months prior to discontinuation, representing over 20% annual growth. If one assumes a conservative 10% growth for 3-4 additional years, one could estimate Zelnorm might have reached over 4 million prescriptions at peak.

Table 28. Zelnorm Montly Prescription Trends



Source: Wolters Kluwer PHAST

Zelnorm's relatively slow onset of action (1-2 weeks vs. 1-3 days for linaclotide), relatively little effect on abdominal pain and bloating, and cardiovascular safety concerns may have impacted market penetration. In fact, roughly 70% of new Zelnorm patients dropped out of therapy after 60 days of therapy and patient adherence approximated 100 days/year. We believe linaclotide will likely have increased patient adherence and capture greater market penetration than Zelnorm's peak potential (if it had not been withdrawn from the market).

Table 29. Linaclotide vs. Zelnorm

	Linaclotide	Zelnorm
Dosing	Once-a-day	Twice-a-day
Systemic absoption	NO	YES
Increased risk of cardiovascular events	NO	YES
Onset of action	1-3 days: The percentages of patients reporting a CSBM within 24 hours of initial dosing ranged from 27% to 37% for the linaclotide dose groups compared to 13% for the placebo group	Approximately 1-2 weeks
Effects on Abdominal Pain	Improvements on a 1-5 point scale: 0.49 for placebo (a 25.6% improvement); -0.90 for 300mcg of linocaltide= a 21.2% greater than in the placebo group	Responders (at least 1 point reduction on a 6 point scale): 1-10% greater than in the placebo group
Effects on Bloating	Improvements on a 1-5 point scale: a 21.2% greater than in the placebo group at the 300mcg dose	Responders (at least 1 point reduction on a 6 point scale): 4-11% greater than in the placebo group

Source: Zelnorm Label and IRWD reports, May 2010

Thus, if one assumes linaclotide usage results in a greater compliance (50-80%) versus Zelnorm and demonstrates greater market penetration, one could argue linaclotide has the potential to generate 6.0 to 7.5 million annual prescriptions. One can adjust the figure down to 6.5 million prescriptions to account for more challenging reimbursement conditions and the presence of Amitiza as competitor.

We project linaclotide will generate 900,000 prescriptions in its second year of commercialization and grow to >6.5 million prescriptions after 5-6 years of commercialization. At a future estimated revenue (to FRX) of >$200 per prescription at peak ($2,500 per patient per year at full compliance and $1,350 with estimated compliance), we believe linaclotide could reach peak revenues of $1.3 to $1.4 billion in the US alone.

Table 30. Linaclotide Prescription Data Model

U.S. IBS-C Script Model	2012E	2013E	2014E	2015E	2016E	2017E	2018E
IBS-C Scripts Dispensed	1,141,522	1,175,768	1,211,041	1,247,372	1,284,793	1,323,337	1,363,037
Potential Additional Prescriptions	40,000	624,232	1,548,959	2,952,628	4,355,207	6,236,663	6,676,963
TOTAL SCRIPTS	1,181,522	1,800,000	2,760,000	4,200,000	5,640,000	7,560,000	8,040,000
Amitiza Annual Scripts	1,087,000	900,000	910,800	1,050,000	846,000	982,800	804,000
Market Share	92%	50%	33%	25%	15%	13%	10%
Linaclotide Scripts	94,522	900,000	1,849,200	3,150,000	4,794,000	6,577,200	7,236,000
IBS-C Market Share	*8%*	*50.0%*	*67.0%*	*75.0%*	*85.0%*	*87.0%*	*90.0%*
Price/Script	$165	$165	$172	$178	$186	$193	$201
Gross Linaclotide Revenues ($M)	$16	$149	$317	$562	$890	$1,270	$1,453

Source: Wolters Kluwer PHAST; Ladenburg Thalmann Estimates

The Amitiza case. Amitiza was approved for the treatment of CC in January 2006. By March 2007 (right before Zelnorm was withdrawn from the market), Amitiza had reached roughly 30,000 prescriptions a month. Following Zelnorm's discontinuation, Amitiza's total prescriptions increased abruptly to 90,000 in April 2007 and monthly new prescriptions increased from 20,000 to 70,000.

Since then, total prescriptions have remained stable at 90,000 per month. However, new prescriptions quickly decreased and settled at 40,000 prescriptions per month. In our view, Amitiza's suboptimal therapeutic profile may help to explain the drug's lack of significant market share gain following the discontinuation of Zelnorm.

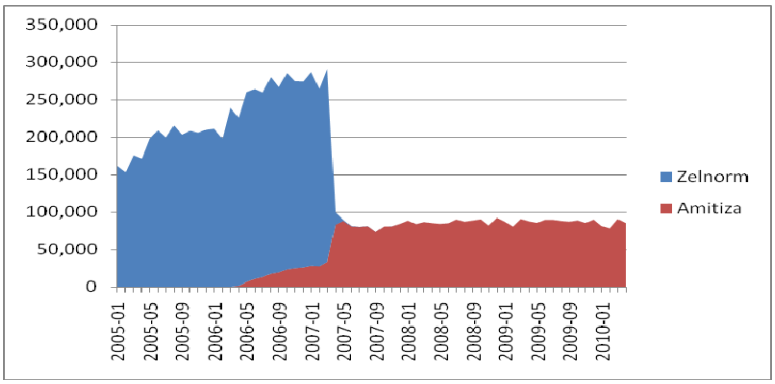
Amitiza was initially approved for CC at 24 µg bid (48µg/day). At this dose, the incidence and severity of nausea (29%) could have limited market penetration (however, we believe some of these effects may be manageable with enhanced physician/patient education). The 8 µg bid (16µg/day) was approved when the label was expanded to include IBS-C. However, at this dose, according to several treating physicians, effects on bowel movements are not as pronounced and the effects on abdominal pain, discomfort and bloating are minimal.

We believe part of Amitiza's substandard results could be due to poor initial marketing and education efforts. Unfortunately, we believe the ongoing litigation between Sucampo Pharmaceuticals, Inc. (NASDAQ: SCMP, not rated, $3.31) and Takeda Pharmaceutical Company may limit the companies' ability to restructure commercial efforts and properly position Amitiza before the introduction of linaclotide.

Finally, Amitiza has a pregnancy category C indicating the drug's teratogenic effects have not been fully characterized in humans. In guinea pigs, linaclotide caused repeat fetal fatalities at doses 2 to 6 times the ones used in humans. In our view, given that the majority of IBS patients are women, this potential liability (a warning in the label) limits market penetration (Amitiza is a prostaglandin derivative).

We also note when Amitiza expanded its label to include IBS-C (April 2008), there was practically no effect on prescription patterns. In our view, this lack of effect can be explained by off label usage in IBS-C, representing the lion's share of Amitiza's prescriptions (pre-label expansion). This case also emphasizes the relative small size of the CC market relative to IBS-C.

Table 31. Amitiza's Reaction Following Zelnom's Withdrawal



Source: Wolters Kluwer PHAST

Synergy Pharmaceuticals (OTCBB: SGYP, not rated, $2.80): SGYP is developing SP-304, a peptide targeting the same receptor (GC-C) as linaclotide. SP-304's value proposition relies on offering similar efficacy to linaclotide with the potential of offering a greater therapeutic margin (since diarrhea is predicated to be unlikely adverse event at therapeutic dose levels). Given the mechanism of action of linaclotide and SP-304 we see a certain level of diarrhea as a "biomarker" of efficacy and we expect a potent drug with significant abdominal and bowel clinical effects to generate a certain degree diarrhea.

In addition, it is unknown whether SP-304 results in greater production of cGMP than linaclotide and whether this will translate into greater abdominal pain and/or bloating benefit.

Phase IIa data in CC (14 days) will be presented (poster presentation) at the American College of Gastroenterology meeting (San Antonio TX, October 15-20, 2010).

SP-304 is >3 years behind linaclotide. Phase IIa data in CC could potentially show the drug's impact in bowel habits. However, the IBS's medical need is in the treatment of abdominal symptoms (pain, bloating). Phase II trials in IBS-C have not started (planned for 2011) and we do not expect proof-of-concept data in IBS-C (12 weeks) in the next 12-24 months.

Pricing considerations: Zelnorm was priced at approximately $5.20 a day (at the time of discontinuation) and Amitiza is priced at $6.30 a day. A monthly prescription of Amitiza is approximately $200 which, according to some gastroenterologists and payers, is perceived as very steep given its therapeutic benefit.

In our opinion, finding the ideal linaclotide pricing represents an important strategic challenge for FRX and IRWD. We believe linaclotide's potential profile and potential for an abdominal pain label claim justify premium pricing. However, we believe formulary adoption, usage by PCPs and use in milder IBS-C cases would benefit from a more moderate pricing strategy. We model initial pricing at $5.50 per day or $165 for every 30 day prescription.

The monthly cost to patients using OTC products typically ranges between $25-$30. In our view, this cost is similar to potential co-payments on a prescription medicine and we believe (assuming insurance coverage) patients would rather take a prescription medicine (linaclotide) that can offer more complete symptomatic benefit.

Commercial Efforts. We expect linaclotide to be launched with the support of approximately 1,100 sales representatives. We believe a sales force of this size can successfully detail roughly 60,000 physicians who are perceived to be potentially high prescribers. We expect IRWD to contribute to up to 35% (initially lower) of the sales detailing and to focus primarily on the gastroenterology market.

FRX's primary contribution in this case is its expertise in the PCP market. However, FRX lacks expertise in the introduction of first in class drugs where there are limited therapeutic alternatives. In addition, FRX also lacks ample expertise in direct to customer promotional activities which are known to be successful in IBS-C.

For this reason, we believe a sophisticated commercial infrastructure needs to be created by IRWD and FRX. The hiring of Thomas A. McCourt as VP of Marketing and Sales and Chief Commercial Officer represents a significant initial effort. Mr. McCourt was a brand manager for Prilosec, launched and managed Zelnorm and recently led the U.S. brand team for denosumab at Amgen Inc. We expect additional announcements in the following quarters with regards to the assembly of a robust commercial team and strategy to support the launch of linaclotide.

We believe the ultimate success of linoclatide will be driven by the ability of the marketing team to create an automatic association in physicians' and patients' mind of abdominal pain with bowel habits. We believe the efforts put into place (if helped by clinical results) should accomplish this goal.

Besides the sales force, we expect significant investment in sampling and medical and consumer education. As seen in Table 32 below, we estimate the total initial sales and marketing expenses to approximate $230 million. Assuming COGS at 7% we estimate linaclotide's US P&L with FRX becomes cash flow even at revenues of $260 to $270 million.

We expect linaclotide's P&L to become profitable in FY 2015 and IRWD's share of profits to reach $478 and $550 million in 2017 and 2018, respectively.

Table 32. Linaclotide IRWD-FRX P&L (Base Case Scenario)

FOREST CO-PROMOTION	2011E	2012E	2013E	2014E	2015E	2016E	2017E	2018E
COGS	$5,000	$1,541	$13,311	$25,206	$39,477	$58,072	$77,055	$87,231
		10%	9%	8%	7%	7%	6%	6%
Marketing & Promotion	20,000	62,000	100,000	90,000	90,000	82,000	75,000	75,000
Sales Force Cost	12,000	135,850	225,055	231,807	207,618	192,462	176,210	181,496
Reps		1,100	1,150	1,150	1,000	900	800	800
Cost per Rep		190	196	202	208	214	220	227
Net Cost of Sales Force to the FRX-IRWD Agreement		81,510	135,033	134,448	120,419	111,628	102,202	105,268
Total SG&A	32,000	143,510	235,033	224,448	210,419	193,628	177,202	180,268
Operating Income	(37,000)	(183,985)	(190,470)	(31,933)	226,856	560,885	955,991	1,110,125
IRWD (50%) Profit Split	(18,500)	(91,993)	(95,235)	(15,966)	113,428	280,442	477,996	555,062
SG&A Reimbursment from FRX	10,000	68,620	88,749	84,911	82,371	79,492	77,147	78,337
Net Cost of Sales Force for IRWD		6,718	13,308	18,847	19,412	19,995	20,595	21,212
TOTAL Payments to Ironwood (Royalty + Reimbursment)	(18,500)	(91,993)	(95,235)	(15,966)	113,428	280,442	477,996	555,062

Source: Ladenburg Thalmann estimates

The worst case scenario assumes the linaclotide label does not include a claim for abdominal pain and only obtains approval for CC and IBS-C (improvement in bowel habit only). If this is the case, assuming lower commercialization expenses, we expect the linaclotide's P&L to become profitable in 2015 and IRWD's share of profits to reach $160 and $170 million in 2017 and 2018, respectively.

Table 33. Linaclotide IRWD-FRX P&L (Worst Case Scenario)

FOREST CO-PROMOTION	2011E	2012E	2013E	2014E	2015E	2016E	2017E
COGS	$5,000	$1,629	$8,576	$16,941	$29,756	$31,726	$36,040
		11%	10%	9%	8%	7%	7%
Marketing & Promotion	35,000	70,000	70,000	65,000	50,000	45,000	45,000
Sales Force Cost	12,000	129,500	133,385	117,760	101,077	104,110	107,233
Reps		700	700	600	500	500	500
Cost per Rep		185	191	196	202	208	214
Net Cost of Sales Force to the FRX-IRWD Agreement		77,700	80,031	70,656	60,646	62,466	64,340
Total SG&A	47,000	147,700	150,031	135,656	110,646	107,466	109,340
Operating Income	(52,000)	(186,324)	(126,197)	(11,471)	191,111	272,390	326,579
IRWD (50%) Profit Split	(26,000)	(93,162)	(63,098)	(5,735)	95,556	136,195	163,289
SG&A Reimbursment from FRX		53,315	53,864	51,930	45,013	43,114	43,732
Net Cost of Sales Force for IRWD		8,177	12,957	13,346	13,747	14,159	14,584
TOTAL Payments to Ironwood (Royalty + Reimbursment)	(26,000)	(93,162)	(63,098)	(5,735)	95,556	136,195	163,289

Source: Ladenburg Thalmann estimates

RISKS INCLUDE, BUT ARE NOT LIMITED TO:

Clinical Risk: Linaclotide is in two pivotal clinical trials for the treatment of IBS-C. The FDA requires two positive clinical trials to prove efficacy and there is a risk linaclotide may fail to demonstrate efficacy in one or both of the studies. Results are expected in 4Q 2010 for the Phase III trials.

Regulatory Risk. IRWD plans to file the NDA for linaclotide in 2H 2011. Assuming positive Phase III trials, we believe the regulatory risk for this program is low given the need for a safe and efficacious drug in IBS-C.

Commercial Risk: IBS-C has traditionally been a difficult indication for prescription medicines. The availability of over the counter medicines coupled with the suboptimal commercial success of existing prescription therapies handicap the market potential of a new entrant Linaclotide may also fail to obtain a label for abdominal pain which could also impede initial sales. Therefore, linaclotide's market penetration could be lower than our estimates.

Partner Risk: FRX is responsible for North American commercialization of linaclotide. FRX does not have experience at commercializing major gastro-intestinal drugs which may require direct to consumer advertisement. Almirall is responsible for the European commercialization of linaclotide. Almirall's sales and marketing efforts may fall short or prove ineffective in promoting the adoption of linaclotide, which would result in royalty revenues below estimates.

Reimbursement Risk. Linaclotide may be unable to obtain favorable formulary placement by third party payers, which could limit initial uptake and patient use.

Financial Risk: IRWD ended Q2 2010 with $299 million. Due to expected milestone payments from IRWD's collaboration agreements, we believe IRWD is unlikely to incur dilution in the near term. However, IRWD could need additional cash to fund its portion of the detailing of linaclotide in the United States.

Additional Risks. Investors should refer to IRWD's SEC filings for further detail on risks associated with investing in IRWD.

Table 34. Quarterly Financial Model ($000s)

	2009A	Q1 '10A	Q2 '10A	Q3 '10E	Q4 '10E	2010E	Q1 '11E	Q2 '11E	Q3 '11E	Q4 '11E	2011E
Collaborative Agreement	$34,321	$8,838	$9,188	$9,341	$9,341	$36,708	9,341	9,341	9,341	9,341	$37,363
Services	1,781	214	1,771	200	200	2,385	300	300	300	300	1,200
Total Revenues	**36,102**	**9,052**	**10,959**	**9,541**	**9,541**	**39,093**	**9,641**	**9,641**	**9,641**	**9,641**	**38,563**
R&D	84,892	18,637	20,953	21,000	17,000	77,590	15,000	12,000	10,000	10,000	47,000
SG&A	23,980	6,643	7,325	8,400	8,400	30,768	9,000	9,500	9,600	9,500	37,600
	1,207										
Operating Expense	**110,079**	**25,280**	**28,278**	**29,400**	**25,400**	**108,358**	**24,000**	**21,500**	**19,600**	**19,500**	**84,600**
Operating Income/Loss	**(73,977)**	**(16,228)**	**(17,319)**	**(19,859)**	**(15,859)**	**(69,265)**	**(14,359)**	**(11,859)**	**(9,959)**	**(9,859)**	**(46,037)**
Other Income											
Interest Income	243	68	189	140	110	507	100	90	95	80	365
Interest Expense	(474)	(93)	(79)	(90)	(90)	(352)	(80)	(80)	(80)	(80)	(320)
Other	600					-					-
Net Loss Attributable to Non-Controlling Interest	2,127	329	73			402					-
Net Non-Operating Income	2,496	304	183	50	20	557	20	10	15	-	45
Pretax Income	**(71,481)**	**(15,924)**	**(17,136)**	**(19,809)**	**(15,839)**	**(68,708)**	**(14,339)**	**(11,849)**	**(9,944)**	**(9,859)**	**(45,992)**
Taxes											
Provison for Income Taxes	296	-	-	-	-	-	-	-	-	-	-
Net Income/Loss	**(71,185)**	**(15,924)**	**(17,136)**	**(19,809)**	**(15,839)**	**(68,708)**	**(14,339)**	**(11,849)**	**(9,944)**	**(9,859)**	**(45,992)**
Earnings/ (Loss) Per Share	**($10.00)**	**($0.25)**	**($0.18)**	**($0.20)**	**($0.16)**	**($0.77)**	**($0.15)**	**($0.12)**	**($0.10)**	**($0.10)**	**($0.47)**
Shares Outstanding (MM)*	7,117	63,958	97,642	97,740	98,300	89,410	98,500	98,650	98,800	98,950	98,725

Source: Corporate Reports and Ladenburg Thalmann & Co estimates.

Table 35. Annual Financial Model ($000s)

	2010E	2011E	2012E	2013E	2014E	2015E	2016E	2017E	2018E
Sales/ Royalties									
US Linaclotide Total Revenues	-	-	15,406	147,896	315,081	563,950	893,419	1,284,256	1,453,852
IRWD Profit Share at 50%	-	-	-	-	-	113,428	280,442	477,996	555,062
SG&A and COGS Reimbursment from FRX	-	-	69,390	95,404	97,514	102,110	108,529	115,675	121,952
		-	69,390	95,404	97,514	215,537	388,971	593,670	677,015
Almirall Royalties	-	-	-	1,697	7,989	25,865	52,011	59,086	67,344
Astella Royalties	-	-	-	-	-	2,700	8,100	12,600	12,600
Other Royalties					1,000	2,160	6,480	10,080	10,080
		-	69,390	97,101	106,503	246,262	455,562	675,437	767,039
Total Sales/Royalties									
Collaborative Arrangement (Forest)	-	25,000	16,300	-	-	-	-	-	-
Collaborative Arrangement (Almirall)	-	9,120	9,120	4,520	-	-	-	-	-
Collaborative Arrangement (Astellas)	-	3,243	3,243	3,243	3,243	3,243	3,243	3,243	3,243
	36,708	37,363	28,663	7,763	3,243	3,243	3,243	3,243	3,243
Services	2,385	1,200	1,000	500					
Total Revenues	39,093	38,563	99,054	105,364	109,746	249,506	458,805	678,680	770,282
% Change		-1.4%	156.9%	6.4%	4.2%	127.3%	83.9%	47.9%	13.5%
COGS	-	-	-	-	-	-	-	-	-
R&D	77,590	47,000	49,000	53,900	56,595	57,444	58,306	59,180	60,068
SG&A			43,240	45,402	47,672	50,056	52,558	55,186	57,946
COGS+SG&A (linaclotide)			76,109	108,712	116,361	121,522	128,523	136,269	143,164
Total SG&A	30,768	37,600	119,349	154,114	164,033	171,578	181,082	191,456	201,110
Other									
Operating Expenses	108,358	84,600	168,349	208,014	220,628	229,021	239,387	250,636	261,178
Operating Income/Loss	(69,265)	(46,037)	(69,295)	(102,650)	(110,882)	20,484	219,418	428,044	509,104
Other Income									
Interest Income	507	365	300	1,000	1,500	1,800	1,800	2,000	2,500
Interest Expense	(352)	(320)	-	-	-	-	-	-	-
Other	-	-	-	-	-	-	-	-	-
	402								
Net Non-Operating Income	$557	45	300	1,000	1,500	1,800	1,800	2,000	2,500
Pretax Income	(68,708)	(45,992)	(68,995)	(101,650)	(109,382)	22,284	221,218	430,044	511,604
Income Tax Paid/(Benefit)	-	-	-	-	-	5,571	66,365	129,013	153,481
Non-Operating Income / (Charge)	-	-	-	-	-	-	-	-	-
Net Income/ (Loss)	**(68,708)**	**(45,992)**	**(68,995)**	**(101,650)**	**(109,382)**	**16,713**	**154,852**	**301,031**	**358,123**
Earnings/ (Loss) Per Share	**(0.77)**	**(0.47)**	**(0.69)**	**(1.01)**	**(1.08)**	**0.16**	**1.51**	**2.92**	**3.45**
Growth Rate									
Shares Outstanding (MM)*	89,410	98,725	100,150	100,750	101,350	101,950	102,550	103,150	103,750
Earnings/ (Loss) - Diluted						**0.16**	**1.43**	**2.77**	**3.28**
Fully Diluted Shares Out (MM)			105,150	105,850	106,550	107,250	107,950	108,650	109,350

Source: Corporate Reports and Ladenburg Thalmann & Co estimates.

APPENDIX A: IMPORTANT RESEARCH DISCLOSURES

ANALYST CERTIFICATION

I, Juan Sanchez, attest that the views expressed in this research report accurately reflect my personal views about the subject security and issuer. Furthermore, no part of my compensation was, is, or will be directly or indirectly related to the specific recommendation or views expressed in this research report.

The research analyst(s) primarily responsible for the preparation of this research report have received compensation based upon various factors, including the firm's total revenues, a portion of which is generated by investment banking activities.

COMPANY BACKGROUND

IRWD is a biopharmaceutical company primarily focused on developing and commercializing of linaclotide for the treatment of IBS-C and CC. Linaclotide is partnered with FRX in the US and Phase III results in IBS-C are expected in Q4 2010.

VALUATION METHODOLOGY

We use a risk-adjusted sum-of-the-parts analysis to value linaclotide.

RISKS

Clinical Risk: Linaclotide is in two pivotal clinical trials for the treatment of IBS-C. The FDA requires two positive clinical trials to prove efficacy and there is a risk linaclotide may fail to demonstrate efficacy in one or both of the studies. Results are expected in 4Q 2010 for the Phase III trials.

Regulatory Risk: IRWD plans to file the NDA for linaclotide in 2H 2011. Assuming positive Phase III trials, we believe the regulatory risk for this program is low given the need for a safe and efficacious drug in IBS-C.

Commercial Risk: IBS-C has traditionally been a difficult indication for prescription medicines. The availability of over the counter medicines coupled with the suboptimal commercial success of existing prescription therapies handicap the market potential of a new entrant Linaclotide may also fail to obtain a label for abdominal pain which could also impede initial sales. Therefore, linaclotide's market penetration could be lower than our estimates.

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Reimbursement Risk: Linaclotide may be unable to obtain favorable formulary placement by third party payers, which could limit initial uptake and patient use.both of the studies. Data from the Phase III program is expected in 4Q 1010.

Commercial Risk: IBS-C has traditionally been a difficult indication for prescription medicines. The availability of over the counter medicines coupled with the suboptimal commercial success of existing prescription therapies handicap the market potential of a new entrant Linaclotide may also fail to obtain a label for abdominal pain which could also impede initial sales. Therefore, linaclotide's market penetration could be lower than our estimates.

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Financial Risk: IRWD ended Q2 2010 with $299 million. We believe IRWD is unlikely to incur dilution in the near term. However, IRWD could need additional cash to fund its portion of the detailing of linaclotide in the United States.

Additional Risks. Investors should refer to IRWD's SEC filings for further detail on risks associated with investing in IRWD.

STOCK RATING DEFINITIONS

Buy: The stock's return is expected to exceed 15% over the next twelve months.
Neutral: The stock's return is expected to be plus or minus 15% over the next twelve months.
Sell: The stock's return is expected to be negative 15% or more over the next twelve months.

Investment Ratings are determined by the ranges described above at the time of initiation of coverage, a change in risk, or a change in target price. At other times, the expected returns may fall outside of these ranges because of price movement and/or volatility. Such interim deviations from specified ranges will be permitted but will become subject to review.

RATINGS DISPERSION AND BANKING RELATIONSHIPS (as of 8/31/10)

Buy	70%	(28% are banking clients)
Neutral	30%	(17% are banking clients)
Sell	0%	(0% are banking clients)

BIOTECHNOLOGY & HEALTHCARE SECTOR STOCKS UNDER AUTHOR ANALYST COVERAGE ("The Universe")

AMAG Pharmaceuticals (AMAG), Cadence Pharmaceuticals (CADX), Chelsea Therapeutics (CHTP), Corcept Therapeutics Inc. (CORT), Cypress Bioscience Inc. (CYPB), Ironwood Pharmaceuticals (IRWD), Micromet Inc. (MITI), Micrus Endovascular Corp (MEND), NeurogesX (NGSX), NeuroMetrix Inc. (NURO), Optimer Pharmaceuticals (OPTR), pSivida (PSDV), Raptor Pharmaceutical Corp. (RPTP), Targacept Inc. (TRGT), Valeant Pharmaceuticals (VRX), XenoPort, Inc. (XNPT), Harris & Harris Group, Inc (TINY).

COMPANY SPECIFIC DISCLOSURES

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