Zacks Small-Cap Research

July 15, 2011
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Transcept Pharmaceuticals, Inc. (TSPT-NASDAQ)

TSPT: FDA Puts Intermezzo To Sleep, Can Management Wake It Back Up?

Current Recommendation	**Neutral**
Prior Recommendation	Outperform
Date of Last Change	07/12/2011
Current Price (07/15/11)	$4.88
Target Price	**$5.00**

UPDATE

Transcept released details of its complete response letter (CRL) received by the U.S. FDA on Intermezzo late on July 14, 2011. Details of the CRL paint a complex and difficult hurdle for management in our view. The FDA has not only proposed some tough questions to answer, but given management little guidance on how to answer them.

The FDA may have put Intermezzo to sleep. Question is, can management wake it back up? On their side is sound scientific rational, a fairly sizable market opportunity, long and defensible IP, and $60 million in cash. Stay tuned.

SUMMARY DATA

52-Week High	**$11.73**
52-Week Low	**$4.73**
One-Year Return (%)	**-39.74**
Beta	**2.21**
Average Daily Volume (sh)	**343,188**
Shares Outstanding (mil)	**13**
Market Capitalization ($mil)	**$64**
Short Interest Ratio (days)	**3.85**
Institutional Ownership (%)	**29**
Insider Ownership (%)	**43**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2010 Estimate	**N/A**
P/E using 2011 Estimate	**N/A**
Zacks Rank	**3**

Risk Level	**Average,**
Type of Stock	**Small-Value**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2010	3.1 A	3.1 A	3.1 A	3.1 A	12.5 A
2011	3.1 A	3.1 E	2.2 E	0 E	8.5 E
2012					0 E
2013					0 E

Earnings per Share
(EPS is operating earnings before non recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2010	-$0.14 A	-$0.15 A	-$0.21 A	-$0.20 A	-$0.69 A
2011	-$0.14 A	-$0.15 E	--$0.21 E	-$0.37 E	-$0.89 E
2012					-$1.03 E
2013					-$0.81 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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WHAT'S NEW

We are going to take a little different approach with this research report. Below, in *gray italic* text, is the press release from Transcept. We've highlighted some key aspects in yellow. Our analysis of what the FDA is saying can be found in regular black text, and where we attempt to prognosticate, we clearly state so with the words "Conclusion" and a fancy looking → before our comments.

CRL Explained

Transcept Pharmaceuticals announced today (July 14, 2011) that is has received a Complete Response Letter (CRL) from the U.S. Food and Drug Administration (FDA) regarding the resubmitted New Drug Application (NDA) for Intermezzo (zolpidem tartrate sublingual tablet).

In the Complete Response Letter, the FDA confirmed that Transcept has adequately demonstrated that Intermezzo is efficacious for use as needed in the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep.

This is pretty simple. It means the FDA is saying the drug works, and no new efficacy studies are required – at least at the 3.5mg dose. We'll get into why we point out this is for the 3.5mg dose only below.

However, the FDA stated that it cannot conclude that Intermezzo can be used safely based on the information in the Intermezzo NDA.

The proposed label for Intermezzo indicates that Intermezzo should only be taken when patients have at least four hours of bedtime remaining before being active again. In the original, October 2009 Complete Response Letter, the FDA indicated that Transcept must demonstrate that Intermezzo, when taken as directed, would not unacceptably impair next-morning driving ability.

To address FDA concerns raised in the October 2009 Complete Response Letter, Transcept and FDA agreed that a highway driving study conducted to assess the effect of Intermezzo on subjects' next-day driving ability would provide a reasonable approach to characterize the safety profile of Intermezzo.

We have the FDA stating the basis of their rejection above, can Intermezzo be used safely? We then have them stating on record what would be a reasonable approach to answering that question.

As previously announced, in the four-hour treatment condition of this highway driving study, the primary analysis used to determine the capacity of Intermezzo to impair driving showed no statistically significant difference between Intermezzo and placebo. In a secondary analysis, the mean effect on driving ability four hours after dosing was statistically different from placebo, but below the level considered in the literature to define the threshold of potential driving impairment.

The primary analysis was the effect of standard deviation of lateral position (SDLP), essentially weaving back and forth, at threshold for driving a one hour on the highway. The study was a double-blind, randomized, placebo-controlled, four-way crossover study of 40 healthy volunteers designed to evaluate the safety profile of Intermezzo with regard to next morning driving. SDLP is a surrogate measure for driving performance.

Subjects drove an automobile 100 km, or 62 miles, on a public highway under normal traffic conditions for approximately one hour. This all took place at the Maastricht University in The Netherlands, a leading center of research on the effects of drugs and alcohol on driving performance.

Management tested patients on a placebo (negative control), 3.5mg Intermezzo at 4 hours post dose (patients got about 3.25 hours of sleep) and 3 hours post dose (patients got about 2.25 hours of sleep), and 7.5mg zopiclone (positive control). As noted in the press release, there was no statistical difference from 3.5mg Intermezzo at 4 hours and the placebo.

	Effect on SDLP At Threshold	Mean Difference From Placebo In SDLP
Placebo	-	-
3.5mg Intermezzo @ 4 hrs	N/S	0.8 cm
3.5mg Intermezzo @ 3 hrs	1.75cm to 4.0cm	1.5 cm
7.5mg zopiclone @ 9 hrs	1.75cm to 5.5cm	2.5 cm

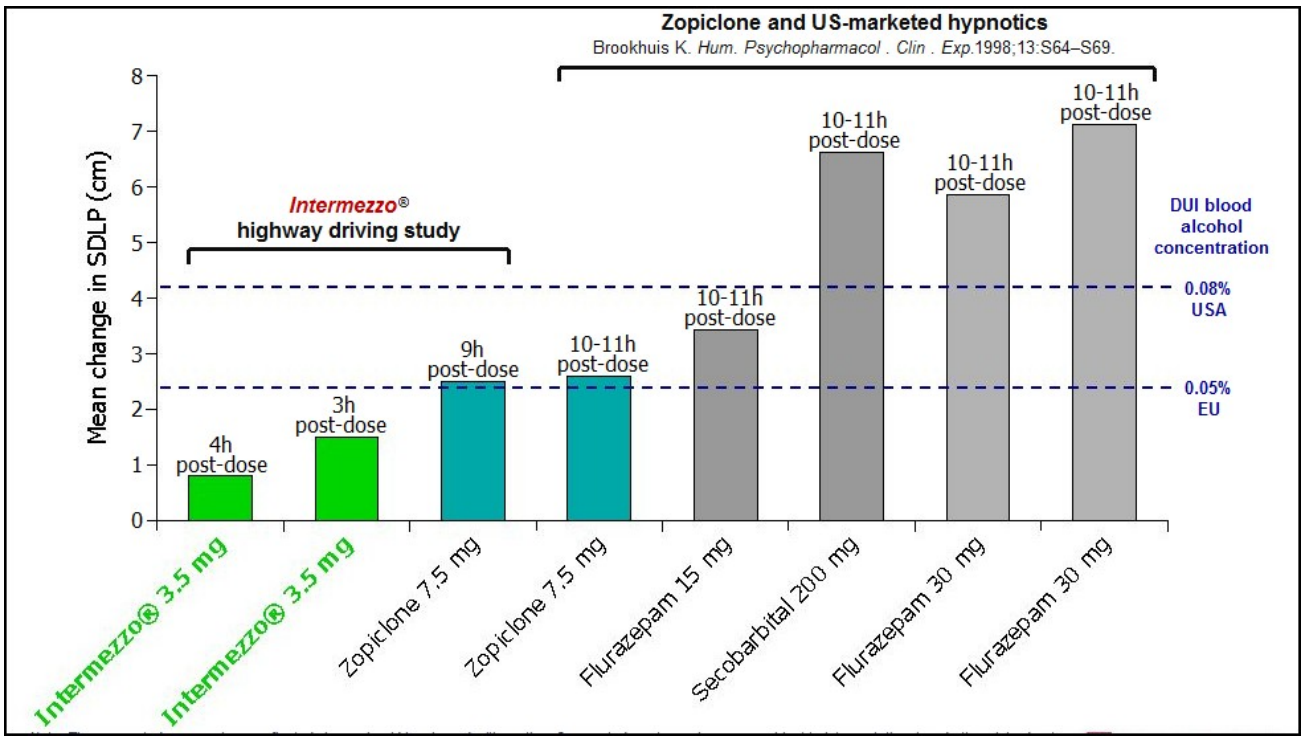
There is no clue determinate on what is safe vs. unsafe SDLP. Therefore, in an attempt to be more thorough in their data analysis, Transcept conducted a secondary analysis looking at the mean difference from placebo in SDLP and the test groups. This symmetry analysis was designed to pick up small differences in variability in lane position that would be masked by a standard mean analysis. In March 2010, the FDA informed Transcept that the statistical methodology proposed by Transcept, this symmetry analysis, was a reasonable approach to measure potential next morning driving impairment. Based on a review of the published literature, an SDLP change of 2.5 cm was specified in the protocol as the primary threshold of impairment for the purpose of performing the statistical analyses.

There was a small statistical difference in the secondary analysis of patients taking 3.5mg Intermezzo at 4 hours vs. the placebo. This difference was 0.8 cm. Transcept concluded that this difference was not clinically meaningful based “available literature”. What Transcept is referring to here are standard safety driving analysis measures that both the U.S. and EU have used to establish blood alcohol content (BAC) maximum thresholds. We are talking about hundreds of millions of dollars, if not billions, that has been spent to determine that a BAC of 0.08% in the U.S. and 0.05% in the EU qualifies as Driving Under the Influence (DUI), and thus unsafe.

For reference, a 0.05% blood alcohol concentration has been associated with a change in SDLP of 2.4 cm, and a blood level of 0.08% has been associated with a mean change in SDLP of 4.2 cm (Brookhuis, Human Psychopharmacology: Clinical and Experimental, Vol. 13, 1998).

So Transcept operated under the Transitive Property here. The U.S. says that at BAC of 0.08% is the minimum level which becomes unsafe. A BAC of 0.08% has been associated with a SDLP of 4.2cm. Therefore, a SDLP under this 4.2cm level should be considered safe. The EU says 0.05% is unsafe, and 0.05% has been associated with a SDLP of 2.4cm. If A = B, and B = Unsafe, then if C < A, C must be safe.

It all makes a little more sense of you view the chart below, which includes positive controls and other approved hypnotic drugs known to cause next-day residual driving issues:



In the Complete Response Letter received today, the FDA stated that during its review of the Intermezzo NDA resubmission it became concerned that those patients with higher zolpidem blood levels from Intermezzo could be at risk of unacceptable next-day impairment. The FDA further hypothesized that such patients may belong to distinct and identifiable demographic groups.

This could mean any number of groups, including characterizing people by weight, ethnicity, gender, and age.

During the review cycle, the FDA requested, and Transcept submitted, analyses of all Intermezzo studies seeking to identify patient sub-populations that may be at risk for elevated blood levels or next-day residual effects.

Transcept received this request several months ago. Instead of conducting the analysis in-house, they outsourced the work to Dr. David J. Greenblatt, Louis Lasagna Professor of Pharmacology and Professor of Psychiatry, Medicine, and Anesthesia, Tufts University School of Medicine. Dr. Greenblatt has authored numerous papers on pharmacokinetics, pharmacodynamics, and drug interactions, and is one of the world's foremost experts on sleep mechanisms, and age and gender effects on the pharmacokinetics for hypnotic drugs. In May 2011, Dr. Greenblatt chaired a session of the FDA/CDER Division of Neurology Products and the Pharmaceutical Education and Research Institute (PERI), which was a two day meeting held to discuss the safety and efficacy of drugs for the treatment of insomnia. Without getting into too much more of Dr. Greenblatt's background, which can be found here: http://www.tuftspharmapartners.org/user/39, this seems like qualified individual.

In these analyses, demographic groups that exhibited higher blood levels were identified, but these blood levels did not correlate with an increase in next-day residual effects as measured by Digit Symbol Substitution Test (DSST), a standard cognitive function test employed by Transcept throughout its development program.

Transcept's conclusion from the data analysis was that no material differences in pharmacokinetics could be identified using the widely-accepted Digit Symbol Substitution Test (DSST). Transcept submitted the data to the FDA per its request. We asked management why they did not report this information to investors, and they responded that since the results were in-line with expectations there was no need to make a material disclosure.

Conclusion → While it might have been nice to know this was going on, we seriously doubt it would have changed perception of Transcept as an investment of Intermezzo's chance at approval, especially after management reported the data shows no material effects through sub-population analysis.

In the Complete Response Letter received today, the FDA expressed the opinion that DSST may not be able to adequately distinguish possible adverse effects of zolpidem on driving ability.

Here's where things get tricky for Transcept. The FDA isn't questioning the data directly; they are questioning the methods in which the data was analyzed. We are not expects in the subject of demographic effects on pharmacokinetics and the Digit Symbol Substitution Test (DSST). Dr. Greenblatt is. Transcept has spoken to other key opinion leaders (KOLs) and the general consensus is that DSST is the best tool for the job. The FDA disagrees, and that creates a major problem for Transcept. The onus is on management to either convince the FDA it is using the right measure or find another widely-accepted measure the FDA will accept.

Conclusion → This is not an easy task. When the smartest guys you know are saying one thing and the FDA is saying another, you have to question the path forward.

In its October 2009 Complete Response Letter, the FDA asked Transcept to demonstrate that inadvertent Intermezzo dosing errors could be adequately minimized, or that the potential adverse effects of such dosing errors on driving safety could be shown to be acceptable. Potential dosing errors cited by FDA as concerns include inadvertent dosing with less than four hours of bedtime remaining and inadvertent re-dosing in a single night. FDA expressed concern that such errors could lead to higher next-day blood levels that could present an unacceptable risk to next-day driving ability.

In the Complete Response Letter received today, the FDA confirmed that the proposed single unit dose pouch packaging adequately addressed the risk of inadvertent re-dosing of Intermezzo in a single night.

Good! This was a silly request from the FDA and we are glad to see it behind Transcept. Inadvertent double-dosing never occurred in the clinical studies and we have the FDA above stating this drug works to put you to sleep. Patients simply are not going to wake up and take another pill an hour later.

However, the FDA remains concerned that some portion of patients will dose with less than four hours remaining in bed, despite proposed packaging and instructions that the FDA viewed as clearly communicating this dosing restriction. The FDA further expressed the view that, while a patient use study to define dosing error rates might be capable of detecting high rates of misuse, such a study would not be required.

We finally put to bed the silly, "patient use study" argument.

Conclusion → The FDA's concerns have little to do with a patient use study. The FDA knows patients are going to incorrectly use the drug. Transcept doesn't need to conduct a study to show that. The FDA wants to know what happens after patients misuse the drug, and what can be done to mitigate the risk.

To address the risk of inadvertent mis-dosing with less than four hours remaining in bed, the FDA believes that driving performance at 3 to 3.5 hours after dosing should be considered as part of the safety review of Intermezzo. To characterize the risk profile of Intermezzo on next-day residual effects if Intermezzo were inadvertently mis-dosed, Transcept assessed subjects' driving ability in a highway driving study beginning at three hours after dosing Intermezzo in the middle of the night.

See the data above.

As previously announced, in drives that started three hours after dosing, Intermezzo was associated with statistically significant effects in the primary analysis, and one drive was discontinued due to excessive driver drowsiness. In a secondary analysis, mean effects on driving ability three hours after dosing were also statistically different from placebo, but were below the level considered in the literature to define the threshold of potential driving impairment.

Again, see the data above. Transcept went back to the transitive property here. Yes, the data show a statistically significant difference between Intermezzo and the placebo at 3 hours post dose, but the effects were below what the literature would consider to be clinically meaningful.

In the Complete Response Letter received today, the FDA stated that these results suggested clinically meaningful impairment.

Here's the kicker…the FDA doesn't agree with the "literature". This is a similar problem to the DSST issue. The best Transcept can do is this transitive property of what is safe vs. unsafe. Dosing Intermezzo and then driving 3 hours shows those drivers are not as impaired as if their BAC was 0.05%. Management inferred this to mean the drug is safe. The FDA doesn't agree.

Conclusion → We don't think Transcept came to a bad conclusion here. We fully admit we came to the same conclusion when we analyzed the data. As noted above, there is no documented change in SDLP that says "safe" vs. "unsafe". It's a gray line. The best we can do is look at historic information and compare the effects of Intermezzo to things that have been well researched, like driving under the influence (DUI) and BAC, and make an assumption on safety by the transitive property. Unfortunately for Transcept, this was not a leap of faith the FDA was willing to take.

As a possible path forward, the FDA suggested that Transcept further investigate whether body weight and demographic factors contribute to differentially elevated blood levels the morning after dosing Intermezzo.

Sounds like a large-scale pharmacokinetic (pk) profiling study.

Conclusion → Not a terrible difficult or expensive to do.

Develop strategies to decrease next-morning zolpidem levels, and, after mitigation strategies are implemented, demonstrate that next-morning blood levels do not present an unacceptable risk of next-day impairment, which may include the conduct of an additional driving study.

This is where it gets difficult again. Transcept is going to have to go back the drawing board on how to come up with these strategies. To us, this sounds like the FDA is asking for a Risk Evaluation and Mitigation Strategy (REMS), although we note that management specifically told us the world "REMS" was never listed in the CRL.

Conclusion → The most logical step we see, if management can identify these sub-populations (by age, weight, race, ethnic background, etc…) is to lower the dose. Transcept has efficacy data testing Intermezzo at 1.75mg. It is possible that 1.75mg may be the new acceptable dose in the eyes of the FDA. Perhaps the drug will be dosed by the pharmacy based on height and weight, or by gender. It's not un-reasonable, considering Ambien (zolpidem) is currently doses at 10mg for adults and 5mg for the elderly. In fact, introducing the 1.75mg dose provides management with further pk separation from 5mg generic zolpidem. Our concern here is that if the FDA does ask for a REMS, or dosing Intermezzo becomes too complicated, it could kill the drug. Intermezzo will most likely be a second-line therapy behind Ambien CR and Lunesta, perhaps even third-line behind Silenor. A restrictive or complicated dosing schedule greatly limits the sales potential of the drug. That being said, simply lowering the dose based on age or weight creates very little to no issues at all. Transcept may have to conduct an efficacy study at 1.75mg just to confirm the use potential, but we see little clinical risk here.

Transcept plans to meet with the FDA to discuss the potential paths forward, and will provide further updates as appropriate.

Conclusion → We think Transcept will probably seek to meet with the FDA sometime during the second half of the year. We expect an update following this face-to-face meeting. If we had to guess, we are looking at probably 18-24 months before a re-submission. Nothing here is overly restrictive from a cost standpoint. Driving studies cost around $1 million, and even a large-scale pk profiling test will only cost a few million. Unless this face-to-face meeting really kills the potential for ever receiving approval with Intermezzo, we are pretty confident management plans to push forward with commercialization.

…What Does Purdue Do…

We remind investors that Purdue Pharma, Transcept U.S. marketing partner, has no ongoing costs associated with the development or intellectual property (IP) protection of Intermezzo. The approval milestone will completely disappear in September 2010, leaving only a $10 million IP transfer milestone and another $80 million in sales-related milestone to come post-approval. At this point, we can only speculate on what Purdue will do. With no ongoing costs and $25 million already paid, it might behoove them to sit around and wait.

…Cash Is King…

Transcept exited the second quarter 2011 with $58.6 million in cash and equivalents. With a burn of around $1.2 million per month, we estimate that Transcept will still hold north of $50 million at the end of 2011. There's no cash crunch that we can see for several quarters, if not years.

Transcept does have a phase 2 candidate in TO-2061 (low-dose ondansetron) for potential use as an adjunctive therapy in adult patients with treatment-resistant obsessive compulsive disorder (TR-OCD) ongoing. TR-OCD is an area with no FDA approved products and significant need. The company may ultimately believe that it is wiser to spend their cash on TO-2061 than continuing to spin their wheels with Intermezzo.

Our Rating is 'Neutral'

We currently rate the shares 'Neutral' with a price target of $5 per share. We have completely removed Intermezzo from our model. We currently do not account for any revenues from Intermezzo or TO-2061 in our model going forward. Our price target is residual cash value.

PROJECTED FINANCIALS

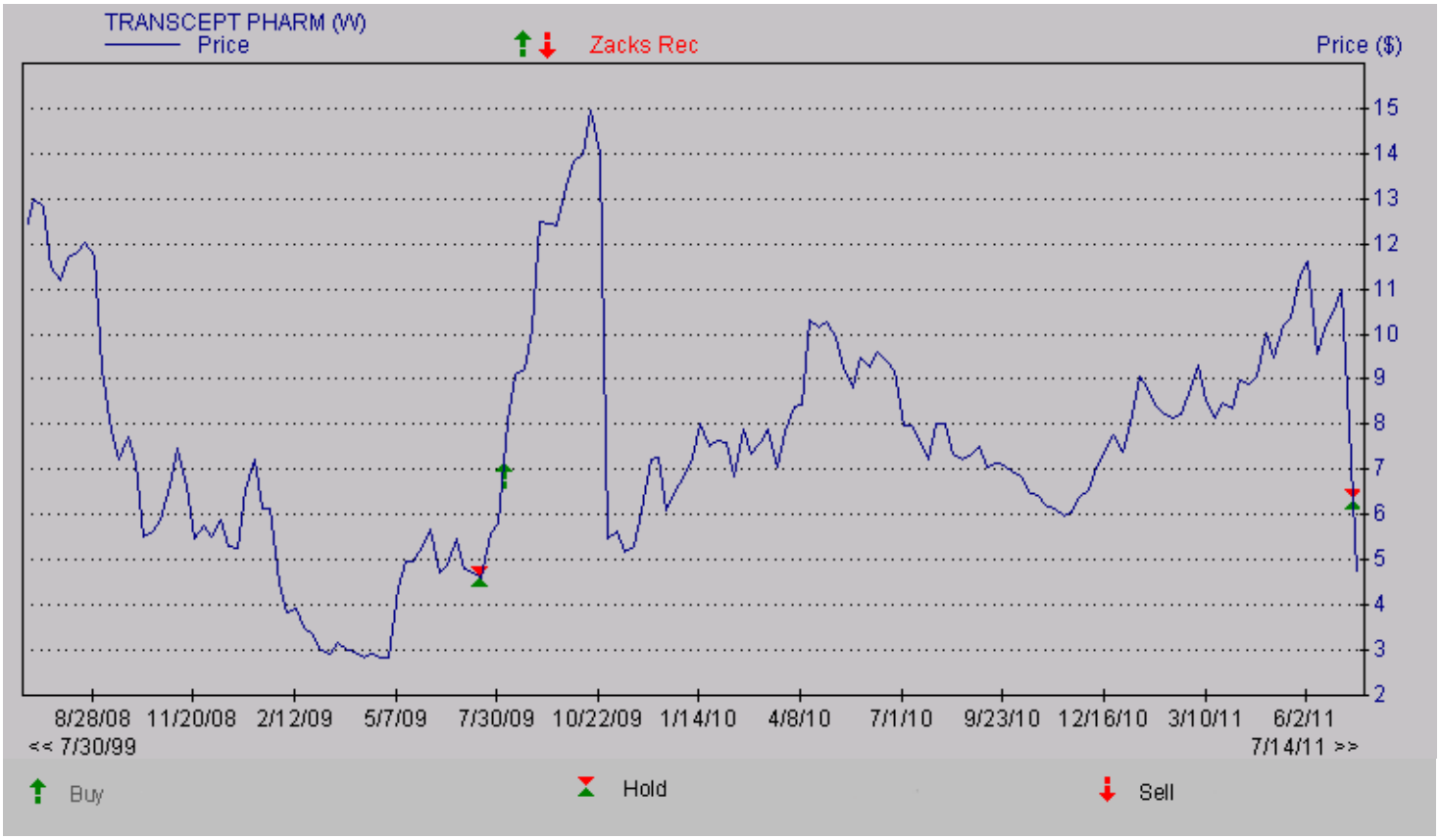
Transcept Pharmaceuticals, Inc.
Income Statement

	2009 A	2010 A	Q1 A	Q2 E	Q3 E	Q4 E	2011 E	2012 E	2013 E	2014 E
Intermezzo (US Sales)	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
Intermezzo (Ex-US Sales)	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
Intermezzo Royalty	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-	-	-
Collaborations / Milestones	**$5.2**	**$12.5**	**$3.1**	**$3.1**	**$2.2**	**$0**	**$8.5**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-	-	-
Setrodon	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-					-	-	-	-
Total Revenues	**$5.2**	**$12.5**	**$3.1**	**$3.1**	**$2.2**	**$0**	**$8.5**	**$0**	**$0**	**$0**
YOY Growth	-	*140.0%*	-	-	-	-	*-32.4%*	*-100.0%*	*-100.0%*	*#DIV/0!*
Cost of Goods Sold	$0	$0	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-	-	-
SG&A	$16.0	$11.0	$2.5	$2.6	$2.5	$2.3	$9.9	$8.5	$9.0	$9.5
% SG&A	*308.0%*	*88.3%*	*81.4%*	*83.2%*	*113.6%*	-	*117.7%*	-	-	-
R&D	$9.0	$10.7	$2.5	$2.6	$2.6	$2.8	$10.5	$10.0	$10.0	$10.0
% R&D	*172.9%*	*85.5%*	*79.7%*	*83.2%*	*118.2%*	-	*124.2%*	-	-	-
Merger & Other Costs	$2.2	$0	$0	$0	$0	$0	$0	$0	$0	$0
Operating Income	($22.1)	($9.2)	($1.9)	($2.1)	($2.9)	($5.1)	($12.0)	($18.5)	($19.0)	($19.5)
Operating Margin	-	-	-	-	-	-	*-141.8%*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*
Interest & Other Net	$0.3	($0.1)	($0.0)	($0.0)	($0.0)	($0.0)	($0.1)	$0.4	$0.5	$0.5
Pre-Tax Income	($21.8)	($9.3)	($1.9)	($2.1)	($2.9)	($5.1)	($12.1)	($18.1)	($18.5)	($19.0)
Taxes / Other	$0	$0	$0	$0	$0	$0	$0	($2.7)	($5.6)	($5.7)
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*15.0%*	*30.0%*	*30.0%*
Net Income	($21.8)	($9.3)	($1.9)	($2.1)	($2.9)	($5.1)	($12.1)	($15.4)	($13.0)	($13.3)
YOY Growth	-	-	-	-	-	-	-	*27.4%*	*7.2%*	*-13.6%*
Net Margin	-	-	-	-	-	-	*-142.9%*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*
Reported EPS	**($1.79)**	**($0.69)**	**($0.14)**	**($0.15)**	**($0.21)**	**($0.37)**	**($0.89)**	**($1.03)**	**($0.81)**	**($0.78)**
YOY Growth	-	-	-	-	-	-	-	*15.8%*	*-8.6%*	*-23.7%*
Shares Outstanding	12.2	13.4	13.5	13.6	13.7	13.8	13.6	15.0	16.0	17.0

Source: Zacks Investment Research, Inc. *Jason Napodano, CFA*

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HISTORICAL ZACKS RECOMMENDATIONS



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