Zacks Small-Cap Research

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Lipocine, Inc. (LPCN - NASDAQ)

LPCN: Positive Phase 3 Data From SOAR Trial!

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	09/24/2014
Current Price (08/18/14)	$7.23
Target Price	**$13.50**

UPDATE

On September 24, 2014, Lipocine, Inc. announced positive top-line results from the Study of Oral Androgen Replacement (SOAR) examining the efficacy of the company's oral testosterone replacement therapy (TRT) LPCN 1021.

The study met both primary endpoints, with 88% of patients attaining normal serum testosterone levels with the lower bound of the 95% confidence interval being 82%. There were no serious adverse events, with data from the full safety study becoming available in the summer of 2015.

The stock rose almost 40% on the news, however we believe the company is still undervalued, thus we are maintaining our 'Buy' rating and a $13.50 price target.

SUMMARY DATA

52-Week High	**$9.88**
52-Week Low	**$5.09**
One-Year Return (%)	**N/A**
Beta	**N/A**
Average Daily Volume (sh)	**73,293**
Shares Outstanding (mil)	**13**
Market Capitalization ($mil)	**$67**
Short Interest Ratio (days)	**1.32**
Institutional Ownership (%)	**28**
Insider Ownership (%)	**14**
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 2014 Estimate	**N/A**
P/E using 2015 Estimate	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2013	$0.0 A	$0.0 A	$0.0 A	$0.0 A	$0.0 A
2014	$0.0 A	$0.0 A	$0.0 E	$0.0 E	$0.0 E
2015					$0.0 E
2016					$0.0 E

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

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2013	-$0.00 A	-$0.00 A	-$0.39 A	-$1.05 A	-$1.44 A
2014	-$0.41 A	-$0.55 A	-$0.58 E	-$0.59 E	-$2.13 E
2015					-$1.89 E
2016					-$1.73 E

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WHAT'S NEW

Lipocine Announces Positive Phase 3 Data for LPCN 1021

On September 24, 2014 Lipocine, Inc. (LPCN) announced positive top-line results for the Study of Oral Androgen Replacement ("SOAR") Phase 3 clinical trial. Overall, the study was a success, showing positive results with respect to the primary efficacy endpoints, no serious adverse events, and generally meeting FDA pre-specified targets for maximum serum concentrations.

…Overview of the Phase 3 trial…

The SOAR trial is a randomized, open-label, parallel-group, active-controlled, Phase 3 clinical trial of the company's oral testosterone replacement therapy (TRT) LPCN 1021. The study enrolled 315 hypogonadal males (serum testosterone < 300 ng/dl) at 40 clinical sites with 210 randomized to LPCN 1021 and 105 randomized to Androgel 1.62%, the active control, for 52 weeks.

Patients in the LPCN 1021 arm were started on 225 of oral testosterone undecanoate (TU; equivalent to approximately 142 mg testosterone) twice daily (BID) at mealtime. At weeks three and seven, patients were dose titrated, if needed, up to 300 mg TU BID or down to 150 TU BID based on serum testosterone level.

The primary endpoints of the study included the percentage of subjects achieving 24-hour average total serum testosterone concentration (Cave) within the normal range for a young, healthy male (300-1140 ng/dl) after completing 13 weeks of treatment along with the lower bound of the 95% confidence interval (CI) for Cave.

Secondary endpoints were based on the maximum serum total testosterone concentration (Cmax) after completing 13 weeks of treatment and included: percentage of subjects who have a Cmax < 1500 ng/dl, percentage of subjects with Cmax between 1800 and 2500 ng/dl, and the percentage of subjects with Cmax >2500 ng/dl.

…LPCN 1021 achieves primary efficacy end points…

Two different statistical analyses were conducted to determine efficacy of LPCN 1021. The primary statistical analysis was conducted using the Efficacy Population Set (EPS), which is defined as subjects randomized into the study with at least one pharmacokinetic (PK) profile and no significant protocol deviations and includes missing data by last observation carried forward (LOCF). This data set included 152 subjects. A second analysis was conducted using the safety set (SS), which included any subject that was randomized into the study and took at least one dose and included imputed missing data by LOCF and treats subjects with no PK data as treatment failures. This data set included 210 subjects.

In the EPS analysis, 88% of subjects on LPCN 1021 achieved serum testosterone Cave within the normal range with a lower bound CI of 82%. These results were confirmed in the SS analysis as 80% of subjects on LPCN 1021 achieved testosterone Cave within the normal range with the lower bound CI of 74%. Thus, even with statistical modeling using the LOCF method, which uses readings from very early in the trial when patients are likely to still have low testosterone and thus not be in the normal range, LPCN still met the FDA guidelines, which are indicated below.

	Typical FDA Targets for Approval of TRT
Dose	
Number of subjects	
Primary endpoints	
Cave 300-1140 ng/dL	≥ 75%
Lower bound 95% CI	≥ 65%
Secondary endpoints	
Cmax < 1500ng/dL	≥ 85%
Cmax 1800-2500ng/dL	≤ 5%
Cmax > 2500ng/dL	0%

***Source*: Lipocine, Inc.**

While not specifically mentioned in the FDA guidelines, examination of additional efficacy data shows that the company was quite accurate with their initial starting dose of 225 mg TU. Over half (51%) of subjects were taking 225 mg BID on their final dose, with 36% on 150 mg BID, and 13% on 300 mg BID. In addition, 85% of subjects arrived at the final dose with no more than one titration. The fact that half of the subjects in the study stayed on the 225 mg dose is likely to be viewed favorably by the FDA.

…Preliminary safety results are encouraging…

The safety component of the SOAR trial is still ongoing and will last a total of 52 weeks. However, preliminary data is encouraging as LPCN 1021 has been well tolerated, with only 3% of patients having experienced a serious adverse event (SAE), none of which were deemed by investigators to be drug related. All drug related adverse events were mild to moderate in nature. Two specific AEs mentioned by the company were one patient who experienced an elevated hematocrit (Hct) and discontinuing treatment and another subject had an elevated prostate specific antigen (PSA) that resulted in their discontinuing from the trial. All other Hct and PSA increases were consistent with other TRT products.

Secondary endpoints examining maximum levels of testosterone were evaluated for the EPS group. The data showed that 83% of subjects had Cmax ≤ 1500 ng/dl, 4.6% of subjects had Cmax between 1800 – 2500 ng/dl, and 2% of subjects. These numbers were quite close, but did not quite reach the required thresholds for Cmax < 1500 ng/dl and Cmax > 2500 ng/dl. While the FDA guidelines call for Cmax > 2500 ng/dl to be 0%, the three patients that had Cmax > 2500 ng/dl were transient, isolated, and not related to dose (two of the patients were on 150 mg and the other patient was on 300 mg LPCN 1021). Thus, we do not believe that this will raise a significant concern with the FDA when the drug comes up for PDUFA review.

…LPCN 1021 data compares very favorably to Rextoro®…

Clarus Pharmaceuticals is developing Rextoro®, an oral formulation of testosterone undecanoate that has been tested in two Phase 3 clinical trials and is currently under review by the FDA. On September 18, 2014 there was a Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) and the Drug Safety and Risk Management Advisory Committee (DSRM) to discuss the new drug application (NDA) submitted for Rextoro®. The outcome of the meeting was decidedly negative for Clarus, as the committee voted 18-3 against recommending Rextoro® for approval. The reasons for this included the small size of the pivotal trial, food effects associated with Rextoro® dosing, a high number of dropouts in the pivotal study, missed secondary endpoints, and a lack of robust efficacy.

The data generated in the SOAR trial compares quite favorably to the data obtained through the two Phase 3 trials of Rextoro®, and while there are some concerns associated with the LPCN 1021 data, we believe the efficacy data is likely to be viewed much more favorably than that presented by Clarus.

Primary Endpoints	FDA Targets for Approval	LPCN 1021 Phase 3	Rextoro Phase 3A	Rextoro Phase 3B*
Cave 300-1140 ng/dl	**≥ 75%**	88%	84%	75%
Lower bound 95% CI	**≥ 65%**	82%	77%	66%
Secondary Endpoints				
Cmax < 1500 ng/dl	**≥ 85%**	83%	59%	81%
Cmax 1800-2500 ng/dl	**≤ 5%**	4.6%	13%	6%
Cmax > 2500 ng/dl	**0%**	2%	14%	3%

*considered pivotal trial

Sources: Lipocine, Inc.; Clarus Therapeutics

In addition, LPCN 1021 reached the primary endpoints while Rextoro® did not after statistical analysis using imputed data.

Primary Endpoints	FDA Targets for Approval	LPCN 1021 LOCF Analysis	Rextoro 3B LOCF Analysis	Rextoro 3B WCS Analysis
Cave 300-1140 ng/dl	**≥ 75%**	80%	71%	60%
Lower bound 95% CI	**≥ 65%**	74%	62%	52%

Sources: Lipocine, Inc.; FDA

…A couple of concerns to keep in mind…

While we feel that overall the data looked very good, there were a few things that the FDA will likely focus on in regards to the primary and secondary endpoints. First, while Lipocine performed a secondary analysis of the primary endpoint data using the LOCF method, the FDA is also likely to analyze the data using the worst-case scenario (WCS) method that was used for analyzing Rextoro®. The WCS method assumes all subjects with missing data are failures, thus it is a very conservative approach because it assumes all missing data were below the threshold for success even though there could be other reasons for the missing data that are unrelated to efficacy. We have no way of performing that analysis at this time, although it is possible it could lead to the percentage of patients falling below the FDA guidelines, which the agency may view unfavorably.

The second thing the FDA may have an issue with is the two secondary endpoints that didn't quite meet the guidelines, as the percentage of subjects with Cmax values < 1500 ng/dl was 83% (FDA guideline is ≥ 85%) and there were 2% of patients with Cmax values > 2500 ng/dl (FDA guideline is 0%). During the Adcom meeting for Rextoro®, the committee did not seem overly concerned with the 3% of patients Clarus reported as having Cmax > 2500 ng/dl, as those readings were transient and did not persist. This also appears to be true for LPCN 1021, as Lipocine stated that the three patients with Cmax values > 2500 ng/dl were "transient, isolated and sporadic." Whether the FDA will take issue with the percentage of patients with Cmax < 1500 ng/dl being 83% instead of 85% is difficult to know, but when examined in the context of all the other data it is unlikely that would keep LPCN 1021 from being approvable.

Lastly, the safety study is still ongoing and will not be completed until the summer of 2015. This data will be absolutely critical for the NDA, and while the preliminary safety data looks good there is no way of knowing for sure if any safety issues will be seen. Based on the fact that Clarus did not report any serious issues with Rextoro®, it is doubtful that any serious unforeseen safety issues will occur with LPCN 1021. However, this is still something to keep in mind, particularly as the FDA is likely to view any TRT with increased scrutiny due to the alleged association of adverse cardiovascular (CV) events with the use of TRT.

Conclusion and Recommendation

We were quite pleased to see positive top-line efficacy results for the SOAR trial, as we had predicted a 75% chance of success. While the Adcom committee voted 18-3 against recommending Rextoro® for approval, we do not feel that this is due to any issues with oral TRT, but rather specific issues related to the data generated from the two Phase 3 trials for Rextoro®. A comparison between LPCN 1021 and Rextoro® shows the data generated by Lipocine to be more robust. In addition, the Rextoro® Adcom committee stated that "…it would be of great value to (hypogonadal) patients to have an oral treatment option…", thus the committee members are quite open to the idea of an oral TRT, but only one that shows the requisite efficacy.

The safety portion of the SOAR study will continue as scheduled with results available by the summer of 2015. We remind investors that Lipocine reported $34 million in cash at the end of the second quarter of 2014, which should be enough to fund the company through the filing of the NDA for LPCN 1021, which is expected to occur in the second half of 2015.

In addition to the SOAR study, Lipocine is continuing work on LPCN 1111, a second-generation TRT with the potential for once daily dosing, as well as LPCN 1107, which is an oral formulation of hydroxyprogesterone caproate (HPC) for the prevention of pre-term birth. The company recently announced the first patient was dosed in the Phase 1 study of LPCN 1107 in pregnant women. Top-line results from this study should be available during 2015.

Following the September 17th Adcomm meeting regarding the appropriate indicated population for TRT as well as the potential for adverse CV outcomes associated with the use of TRT investors were decidedly negative, sending Lipocine's stock down over 30%. However, investors were quite pleased by the Phase 3 data that Lipocine presented, as the stock was up over 30% after the data was released. The large increase in share price has simply eliminated the decrease that occurred due to the negative sentiment following the September 17th Adcomm meeting. This means that Lipocine is still undervalued, thus we are keeping a Buy rating on the stock and our $13.50 price target in place.

PROJECTED FINANCIALS

Lipocine, Inc.
Income Statement

Lipocine Incorporated	2013 A	Q1 A	Q2 A	Q3 E	Q4 E	2014 E	2015 E	2016 E
LPCN 1021	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**
YOY Growth		-	-	-	-	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*
LPCN 1111	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**
YOY Growth								
LPCN 1107	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**
YOY Growth								
Total Revenues	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**	**$0.0**
CoGS	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Gross Income	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Product Gross Margin	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*
R&D	$5.1	$3.4	$6.0	$6.0	$6.3	$21.6	$25.0	$27.0
% R&D	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*
SG&A	$3.6	$1.9	$1.0	$1.5	$1.6	$6.1	$9.0	$11.0
% SG&A	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*
Other expenses	$1.9	$0.0	$0.0	$0.0	$0.0	$0.0	$0.1	$0.1
Operating Income	($10.7)	($5.3)	($7.0)	($7.5)	($7.9)	($27.7)	($34.1)	($38.1)
Operating Margin	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*	*#DIV/0!*
Total Other Income	$0.0	$0.0	$0.0	$0.0	$0.0	$0.1	$0.0	$0.0
Pre-Tax Income	($10.6)	($5.3)	($7.0)	($7.5)	($7.9)	($27.6)	($34.1)	($38.1)
Taxes & Other	$0.1	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*99%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	($10.6)	($5.3)	($7.0)	($7.5)	($7.9)	($27.6)	($34.1)	($38.1)
Reported EPS	**($1.44)**	**($0.41)**	**($0.55)**	**($0.58)**	**($0.59)**	**($2.13)**	**($1.89)**	**($1.73)**
YOY Growth	-	-				-		-
Shares Outstanding	7.4	12.7	12.8	13.0	13.5	13.0	18.0	22.0

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

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