Zacks Small-Cap Research

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Grant Zeng, CFA
312-265-9466
gzeng@zacks.com

scr.zacks.com
10 S. Riverside Plaza, Chicago, IL 60606

Threshold Pharm (THLD-NASDAQ)

THLD: Two Phase III trials of evofosfamide failed, focus shifted to TH-4000---Hold

Current Recommendation	**Hold**
Prior Recommendation	Buy
Date of Last Change	12/07/2015
Current Price (12/07/15)	$0.60
Target Price	**$1.00**

OUTLOOK

Threshold just announced the results of two Phase III studies of its lead candidate evofosfamide, which failed to demonstrate statistically significant improvement of OS in soft tissue sarcoma and pancreatic cancer respectively.

Focus is shifted to the new candidate TH-4000. Two Phase II trials are initiated for TH-4000 in 3Q15.

We downgrade THLD shares to Hold from previous Buy based on the disappointed Phase III data.

SUMMARY DATA

52-Week High	**$5.11**
52-Week Low	**$2.91**
One-Year Return (%)	**3.73**
Beta	**2.92**
Average Daily Volume (sh)	**830,067**
Shares Outstanding (mil)	**71**
Market Capitalization ($mil)	**$239**
Short Interest Ratio (days)	**11.11**
Institutional Ownership (%)	**N/A**
Insider Ownership (%)	**N/A**
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**
Zacks Rank	**N/A**

Risk Level	**Above Avg.,**
Type of Stock	**N/A**
Industry	**Med-Biomed/Gene**
Zacks Rank in Industry	**N/A**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	3.7 A	3.7 A	3.7 A	3.7 A	14.7 A
2015	3.7 A	3.7 A	3.7 A	3.7 E	14.7 E
2016					5.00 E
2017					5.00 E

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

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	-$0.14 A	-$0.12 A	-$0.13 A	-$0.09 A	-$0.48 A
2015	-$0.17 A	-$0.12 A	-$0.09 A	-$0.08 E	-$0.45 E
2016					-$0.42 E
2017					-$0.51 E

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

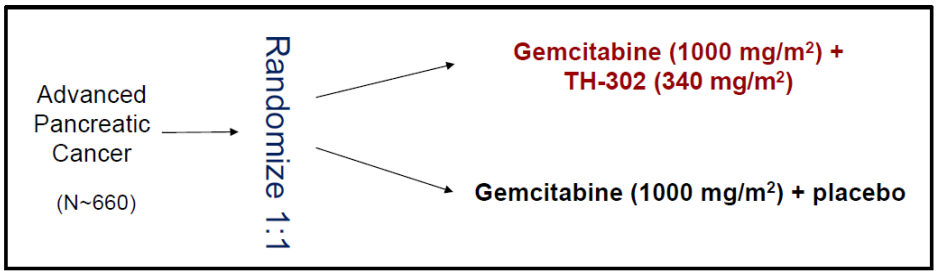
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WHAT'S NEW

THLD Reports Disappointing Phase III Results

Earlier this morning, Threshold (THLD) announced the outcomes of two **Phase III** cancer studies (MAESTRO and TH-CR-406/SARC021) of evofosfamide (TH-302).

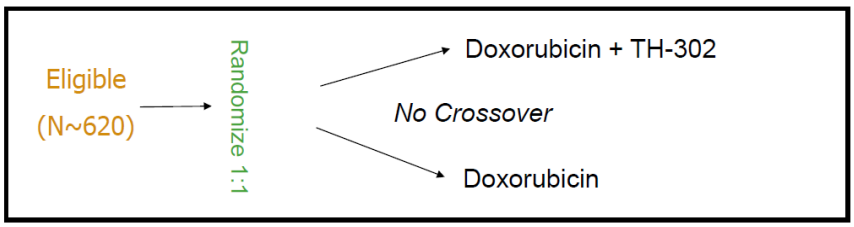
The first Phase III study is **MAESTRO,** which is a randomized, placebo-controlled, international, multi-center, double-blind Phase III clinical trial of EVOFOSFAMIDE plus gemcitabine compared with placebo plus gemcitabine in patients with previously untreated, locally advanced unresectable or metastatic **pancreatic adenocarcinoma.** The trial enrolled about 660 patients. The primary efficacy endpoint is overall survival; the secondary endpoints include efficacy measured by progression-free survival, overall response rate and disease control rate, as well as assessments of safety and tolerability, pharmacokinetics and biomarkers. The study is being conducted under an **SPA** with the FDA.



Patients	Metastatic or locally advanced unresectable pancreatic cancer
Primary Endpoint	Overall survival (OS)
Secondary Endpoints	Overall response rate, progression free survival, CA19-9, QOL, pain, safety

This study **did not** demonstrate a statistically significant improvement in overall survival (OS) compared with gemcitabine plus placebo (hazard ratio [HR]: 0.84; 95% confidence interval [CI]: 0.71 - 1.01; p=0.0589).

The second Phase III trial is **TH-CR-406/SARC021**, which evaluates evofosfamide in combination with doxorubicin in patients with locally advanced unresectable or metastatic **soft tissue sarcoma**. This study also failed to achieve a statistically significant improvement in OS compared with doxorubicin alone (HR: 1.06; 95% CI: 0.88 - 1.29).



Patients	Metastatic or locally advanced unresectable front-line soft tissue sarcoma
Primary Endpoint	Overall survival (OS); 85% power to detect 33% improvement (434 events)
Secondary Endpoints	Overall response rate, progression free survival, duration of response, QOL

Both Phase III studies are being conducted under Threshold's collaboration with Merck KGaA, Darmstadt, Germany. The TH-CR-406/SARC021 study is also being conducted in collaboration with the Sarcoma Alliance for Research through Collaboration (SARC).

Safety was monitored in MAESTRO and TH-CR-406/SARC021 by independent data monitoring committees throughout the conduct of each study. No new clinically significant safety findings were observed.

Detailed results from both studies are still unknown at this time, but will be submitted for presentation at upcoming international scientific meetings and for publication in peer-reviewed journals.

Based on these negative results, Threshold will not be pursing further development of evofosfamide in soft tissue sarcoma and pancreatic cancer according to management.

Focus will be Shifted to Tarloxotinib Bromide (TH-4000)

With the failure of evofosfamide in soft tissue and pancreatic cancer, focus will be shifted to the development of Tarloxotinib.

Two Phase II Trials of Tarloxotinib Initiated in 3Q15

Based on positive preclinical and Phase I clinical data, THLD initiated two **Phase II** trials of Tarloxotinib (TH-4000) in 3Q15.

The first Phase II trial is for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck **(SCCHN)** or skin **(SCCS).**

This is a single-arm, open label study that will enroll up to **68 patients** with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) or skin (SCCS). Eligible patients will receive tarloxotinib (150 mg/m^2 by intravenous infusion) on Days 1, 8, 15 and 22 of a 28-day cycle. Prior anti-EGFR antibody therapy is permitted.

RECIST response rate is the **primary endpoint**. Secondary endpoints include duration of response, progression-free survival, overall survival, safety, tolerability and pharmacokinetics. In addition to other target-specific biomarkers, hypoxia status will be measured at baseline using Threshold's proprietary PET imaging agent [18F]-HX4. The study is planned to be opened at 10 sites in the U.S. and Australia.

Top line data are expected to be available **in early 2017**.

The second Phase II trial is in patients with EGFR-Mutant, T790M-Negative, Advanced non-small cell lung cancer **(NSCLC).**

This is a single-arm, open label study that will enroll up to 37 patients with Stage IV NSCLC who have a sensitizing EGFR mutation and who have progressed on EGFR tyrosine kinase inhibitor therapy (with no intervening therapy), and who subsequently test negative for the T790M mutation on post-progression biopsy. Eligible patients will receive tarloxotinib (150 mg/m^2 by intravenous infusion) on Days 1, 8, 15 and 22 of a 28-day cycle.

The primary objective is overall response rate. Secondary objectives include safety and tolerability, PK and pharmacodynamic relationships, duration of response, PFS and OS. Hypoxia status will be measured at baseline. The study will be open at 12 sites in the U.S. and Australia and top line data are expected in **late 2016**.

We believe both indications represent significant unmet medical needs. The license of TH-4000 is a natural expansion of the Company’s clinical pipeline, which diversify its clinical risks in our view.

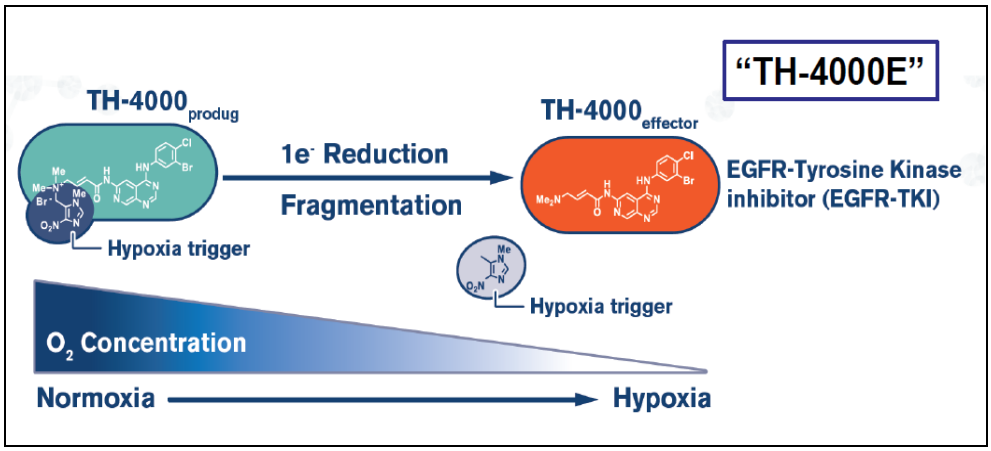
The Background of TH-4000

In September, 2014, Threshold licensed **TH-4000** (formerly known as PR610 or Hypoxin**)** from the University of Auckland of New Zealand.

TH-4000 is a hypoxia-targeted epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor (TKI). In hypoxic tumors, TH-4000 will selectively release a potent, picomolar, irreversible EGFR-TKI.

TH-4000 is a small molecule prodrug that releases the potent EGFR-TKI via reductases under hypoxic conditions which exist in most cancer cells. When TH-4000 enters the tumor cells, it diffuses to the hypoxic zone, in which the TH-4000 effector (TH-4000E) is selectively activated and blocks hypoxia-induced EGFR signaling and tumor cell survival.

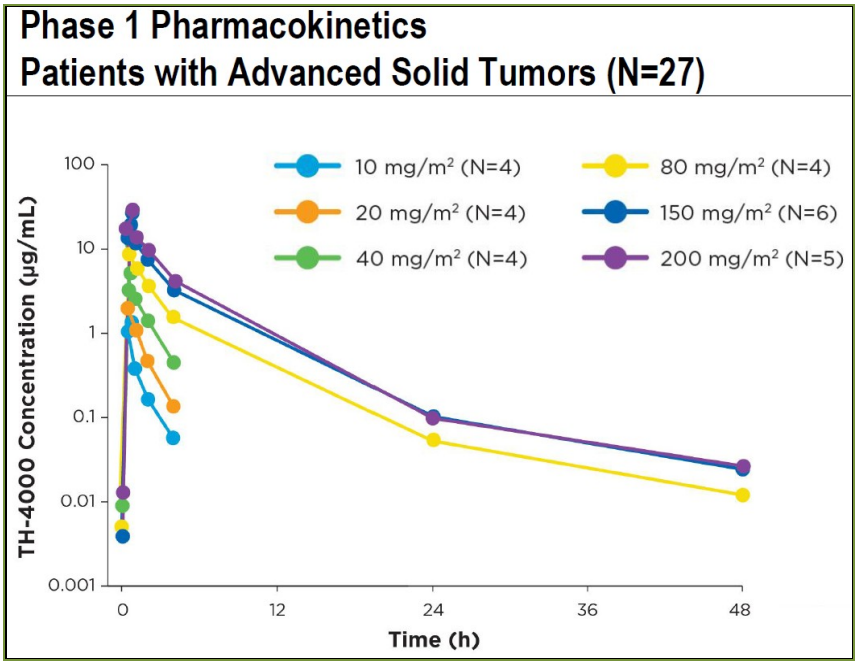
EGFR signaling is involved in the growth and spread of certain tumor types including non-small cell lung cancer (NSCLC) and head and neck cancer (H&N). Clinical studies indicate that mutant EGFR-positive NSCLC with wild-type EGFR present (heterozygous) is associated with reduced response rates, progression free survival and overall survival outcomes on conventional EGFR-TKIs. In H&N cancer, wild-type EGFR signaling drives tumor growth. Both types of tumors are known to be hypoxic; thus, hypoxia-induced activation of wild-type EGFR signaling may be a mechanism of current EGFR-TKI resistance.



Phase I Clinical Studies of TH-4000 for Cancers

The completed Phase I trial enrolled 27 patients with advanced solid tumors. TH-4000 was administered as a 1-hour weekly intravenous infusion.

The maximum tolerated dose of TH-4000 was established at 150 mg/m^2. The most common treatment-related adverse events were dose-dependent and included rash, QT prolongation, nausea, infusion reaction, vomiting, diarrhea and fatigue.



Update on Ongoing Phase I/II Trial of EVOFOSFAMIDE for MM

Recently, Threshold Pharmaceuticals presented updated preliminary data from the **Phase II component** of an ongoing Phase I/II trial of **EVOFOSFAMIDE** (TH-302) in combination with bortezomib (Velcade®) and low-dose dexamethasone (EBorD)for the treatment of patients with relapsed/refractory multiple myeloma **(MM)** at different scientific meetings including ASCO and the 56th ASH Annual Meeting.

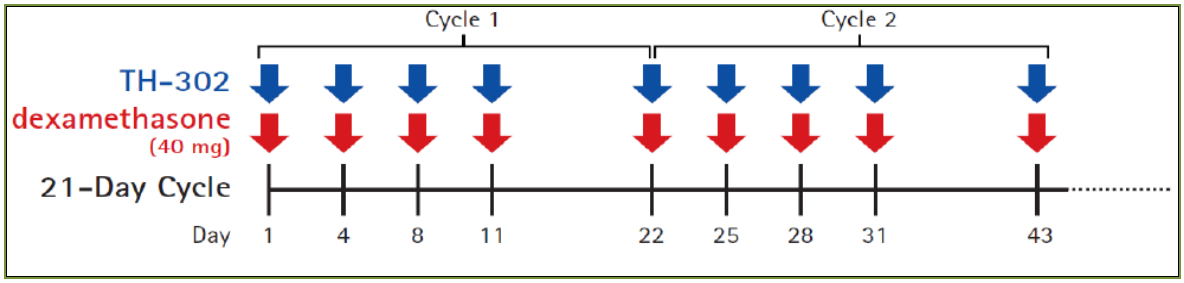
Background

In March 2012, Threshold initiated a **Phase I/II** (the 408 trial) open label clinical trial of EVOFOSFAMIDE with **relapsed/refractory multiple myeloma**.

The study has three parts:

- The first part is designed to establish the maximum tolerated dose of EVOFOSFAMIDE **in combination with dexamethasone**; completed;
- This MTD of EVOFOSFAMIDE will be further evaluated in combination with dexamethasone in additional patients in the second part of the study; ongoing;
- Lastly, the combination of EVOFOSFAMIDE and dexamethasone with **Velcade**® (bortezomib, a proteasome inhibitor currently used to treat patients with multiple myeloma) will be investigated, initiated in July 2014.

The dose of EVOFOSFAMIDE administered in the dose escalation portion of the study was 240, 340, or 480 mg/m^2 given on days 1, 4, 8, and 11 of a 21-day cycle, with 40 mg dexamethasone given on the same days as EVOFOSFAMIDE.



The first part dose escalation of the Phase I/II trial has been completed. **14 patients** received therapy. These patients were heavily pretreated having received 3 to 11 prior treatments (median of 6.5) and all having received a regimen containing bortezomib, an immunomodulatory agent lenalidomide and/or thalidomide, and an alkylating agent. Patients received one to 19 cycles (median of 4 cycles) of therapy with EVOFOSFAMIDE and dexamethasone. **The maximum tolerated dose** was determined to be **340 mg/m^2** EVOFOSFAMIDE. The most frequent Grade 3/4 side effects were thrombocytopenia, leukopenia, anemia, and neutropenia.

Updated Data from Phase II Portion in Multiple Myeloma at ASCO

A total of 18 patients were included in the ASCO presentation. Preliminary results suggested anti-myeloma activity of EBorD therapy. A clinical **benefit rate of 29%** (one complete response, two partial responses, and one minimal response) was observed in 14 patients treated at the recommended Phase II dose of evofosfamide (340 mg/m^2) in EBorD. Objective responses were observed in heavily pretreated patients (median of 8 prior systemic therapy regimens) including prior treatment with bortezomib (median of 3 prior bortezomib-containing regimens). Eleven patients achieved stable disease (SD). Three patients had progressive disease (PD).

Preliminary safety and tolerability results from the 18 patients included in the ASCO presentation support further investigation of evofosfamide in patients with relapsed/refractory multiple myeloma. The most common Grade 3/4 hematological adverse events were thrombocytopenia (reported in 11 patients), anemia (reported in 6 patients), and neutropenia (reported in 4 patients). Nausea (reported in 8 patients; one Grade 3/4) and fatigue (reported in 7 patients; one Grade 3/4) were the most common non-hematological adverse events. Eleven serious adverse events (SAEs) were reported in 9 patients. The only SAE occurring in more than one patient were two events of colitis. Neither event was considered related to evofosfamide. Five SAEs were considered as related to evofosfamide: bronchiolitis, melena, pneumonia, thrombocytopenia and viral infection. Skin toxicity and mucosal toxicities were not dose limiting. Rash was reported in five patients; stomatitis, skin lesion, pruritus and skin hyperpigmentation were each reported in one patient; none of these were Grade 3 or higher. No patients discontinued treatment due to an adverse event. There were no deaths related to study drug.

We think these initial responses to EBorD therapy are encouraging given that these patients had progressive disease despite having received multiple types of treatment prior to enrollment in this study. We are also pleased with the initial safety and tolerability assessments of the TBorD regimen.

There are few treatment options for patients with advanced multiple myeloma that stop responding to bortezomib and lenalidomide, and responses to subsequent salvage therapy have historically been extremely low. The preliminary results suggest that the combination of EVOFOSFAMIDE with dexamethasone is active in some heavily pretreated patients who have failed conventional therapy.

We Downgrade THLD Shares to Hold from Previous Buy Rating

We are surprised and disappointed that these two Phase III failed to replicate the results from previous Phase II studies and did not demonstrate statistically significant improvement in OS.

Based on the current situation, we downgrade THLD shares to Hold from previous Buy rating. Our new price target is $1.00 per share.

At this time, we don't know the detailed data from both Phase III trials, but from the **MAESTRO** trial**,** we still see a P value of 0.0589, close to the significance of 0.05. Therefore, at this point, we are not sure if the failure is related to the trial design or the molecule itself. There are still three mid-stage trials ongoing from the hypoxia platform.

In addition to EVOFOSFAMIDE, Threshold is also developing **TH-4000** for cancers, which naturally expand its clinical pipeline. TH-400 is currently in two Phase II clinical trials.

The failure of the two Phase III trials certainly hurts the collaboration with Merck KGaA. We expect Merck KGaA to announce termination of the collaboration soon.

As of September 30, 2015, Threshold had $56.4 million in cash, cash equivalents and marketable securities. We estimate current cash balance could last into 2017.

Our new price target of $1.00 per share values the company at $71 million in market cap based on 71 million outstanding shares.

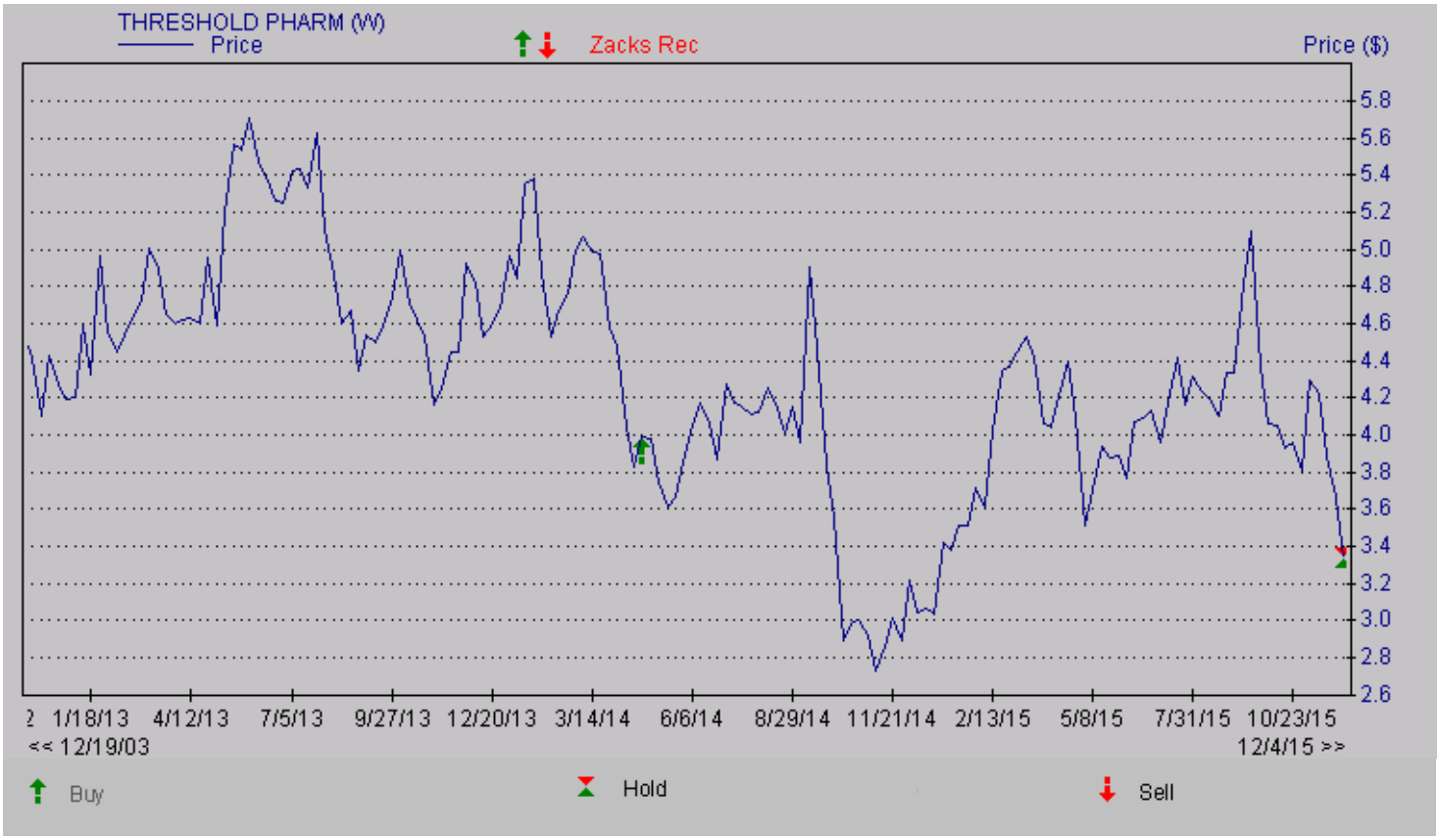
PROJECTED INCOME STATEMENT

	2014A (Dec)					2015E (Dec)					2016E (Dec)	2017E (Dec)	2018E (Dec)	2019E (Dec)
$ in million except per share data	Q1A	Q2A	Q3A	Q4A	FYA	Q1	Q2	Q3	Q4	FYE	FYE	FYE	FYE	FYE
Collaboration revenue	$3.68	$3.68	$3.68	$3.68	$14.72	$3.68	$3.68	$3.68	$3.68	$14.72	$5.00	$5.00	$5.00	$5.00
Product revenue	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$5.00
Total Revenues	**$3.68**	**$3.68**	**$3.68**	**$3.68**	**$14.72**	**$3.68**	**$3.68**	**$3.68**	**$3.68**	**$14.72**	**$5.00**	**$5.00**	**$5.00**	**$10.00**
YOY Growth	26.0%	15.7%	15.7%	14.6%	17.8%	0.0%	0.0%	0.0%	0.0%	0.0%	-66.0%	0.0%	0.0%	100.0%
CoGS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.75
Gross Income	**$3.68**	**$3.68**	**$3.68**	**$3.68**	**$14.72**	**$3.68**	**$3.68**	**$3.68**	**$3.68**	**$14.72**	**$5.00**	**$5.00**	**$5.00**	**$9.25**
Gross Margin	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	92.5%
R&D	$9.65	$8.66	$8.91	$8.61	$35.83	$10.68	$10.14	$8.08	$7.00	$35.90	$25.00	$30.00	$35.00	$50.00
% R&D	262.2%	235.4%	242.0%	233.9%	243.4%	290.1%	275.6%	219.6%	190.2%	243.9%	500.0%	600.0%	700.0%	500.0%
SG&A	$2.63	$2.48	$2.41	$2.62	$10.14	$2.62	$2.48	$2.37	$2.50	$9.97	$11.00	$13.00	$15.00	$17.00
%SG&A	72%	67%	65%	71%	69%	71%	67%	64%	68%	68%	220%	260%	300%	170%
Other	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Operating Income	**($8.6)**	**($7.5)**	**($7.6)**	**($7.6)**	**($31.3)**	**($9.6)**	**($8.9)**	**($6.8)**	**($5.8)**	**($31.1)**	**($31.0)**	**($38.0)**	**($45.0)**	**($57.8)**
Operating Margin	-	-	-	-	-	-	-	-	-	-	-	-	-	-577.50%
Other Net	$1.5	$6.7	($0.3)	$1.6	$9.5	($1.5)	$0.6	$0.3	$0.0	($0.6)	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	**($7.1)**	**($0.8)**	**($7.9)**	**($6.0)**	**($21.8)**	**($11.2)**	**($8.3)**	**($6.4)**	**($5.8)**	**($31.7)**	**($31.0)**	**($38.0)**	**($45.0)**	**($57.8)**
Income taxes(benefit)	$0.0	$0.0	($0.2)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Reported Net Income	**($7.1)**	**($0.8)**	**($7.7)**	**($6.0)**	**($21.8)**	**($11.2)**	**($8.3)**	**($6.4)**	**($5.8)**	**($31.7)**	**($31.0)**	**($38.0)**	**($45.0)**	**($57.8)**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Net Margin	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diluted Shares Out	61.3	63.0	61.5	63.5	62.3	66.7	72.8	71.4	73.2	71.0	74.0	75.0	78.0	80.0
Reported EPS	**($0.12)**	**($0.01)**	**($0.13)**	**($0.09)**	**($0.35)**	**($0.17)**	**($0.11)**	**($0.09)**	**($0.08)**	**($0.45)**	**($0.42)**	**($0.51)**	**($0.58)**	**($0.72)**
One-time charge	*($1.50)*	*($6.67)*	*$0.00*	*$0.00*	*($8.16)*	*$0.00*	*($0.60)*	*$0.00*	*$0.00*	*-$0.60*	*$0.00*	*$0.00*	*$0.00*	*$0.00*
Non GAAP Net Income	**($8.6)**	**($7.4)**	**($7.7)**	**($6.0)**	**($30.0)**	**($11.2)**	**($8.9)**	**($6.4)**	**($5.8)**	**($32.3)**	**($31.0)**	**($38.0)**	**($45.0)**	**($57.8)**
Non GAAP EPS	**($0.14)**	**($0.12)**	**($0.13)**	**($0.09)**	**($0.48)**	**($0.17)**	**($0.12)**	**($0.09)**	**($0.08)**	**($0.45)**	**($0.42)**	**($0.51)**	**($0.58)**	**($0.72)**

Source: company filings and Zacks estimates

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Hold/Neutral: The analyst expects that the company will perform in line with the broader U.S. equity market over the next one to two quarters.
Sell/Underperform: The analyst expects the company will underperform the broader U.S. Equity market over the next one to two quarters.

The current distribution is as follows: Buy/Outperform- 15.9%, Hold/Neutral- 78.2%, Sell/Underperform – 5.7%. Data is as of midnight on the business day immediately prior to this publication.