Zacks Small-Cap Research
Sponsored – Impartial - Comprehensive

May 27, 2020
David Bautz, PhD
312-265-9471
dbautz@zacks.com

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

Essa Pharma Inc

(EPIX-NASDAQ)

EPIX: Additional Preclinical Data Presented at AUA 2020…

Based on our probability adjusted DCF model that takes into account potential future revenues from EPI-7386, EPIX is valued at $10.50/share. This model is highly dependent upon continued clinical success of EPI-7386 and will be adjusted accordingly based upon future clinical results.

Current Price (05/27/20)	$5.20
Valuation	**$10.50**

OUTLOOK

On May 15, 2020, ESSA Pharma Inc. (EPIX) announced new preclinical data was presented at the 2020 American Urological Association Annual Meeting. Included in the data set was a characterization of the effect of EPI-7386 on gene expression in comparison to enzalutamide and combination treatment with both compounds. In addition, new toxicology data shows that EPI-7386 achieves very high plasma exposure and is well tolerated at doses that are 2-5 fold higher than the efficacious exposure levels achieved in mouse xenograft models. The company recently announced the IND for EPI-7386 was accepted by the FDA and a Phase 1 clinical trial will initiate soon in patients with metastatic castration resistant prostate cancer.

SUMMARY DATA

52-Week High	**$6.00**
52-Week Low	**$1.46**
One-Year Return (%)	**152.20**
Beta	**1.65**
Average Daily Volume (sh)	**27,586**
Shares Outstanding (mil)	**21**
Market Capitalization ($mil)	**$107**
Short Interest Ratio (days)	**1**
Institutional Ownership (%)	**67**
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 2020 Estimate	**-4.1**
P/E using 2021 Estimate	**-5.4**

Risk Level	**Below Avg.**
Type of Stock	**Small-Blend**
Industry	**Med-Drugs**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2019	0 A	0 A	0 A	0 A	0 A
2020	0 A	0 A	0 E	0 E	0 E
2021					0 E
2022					0 E

Earnings per Share

	Q1 (Dec)	Q2 (Mar)	Q3 (Jun)	Q4 (Sep)	Year (Sep)
2019	-$0.42 A	-$0.54 A	-$0.52 A	-$0.07 A	-$1.24 A
2020	-$0.22 A	-$0.45 A	-$0.16 E	-$0.16 E	-$1.03 E
2021					-$0.53 E
2022					-$0.54 E

© Copyright 2019, Zacks Investment Research. All Rights Reserved.

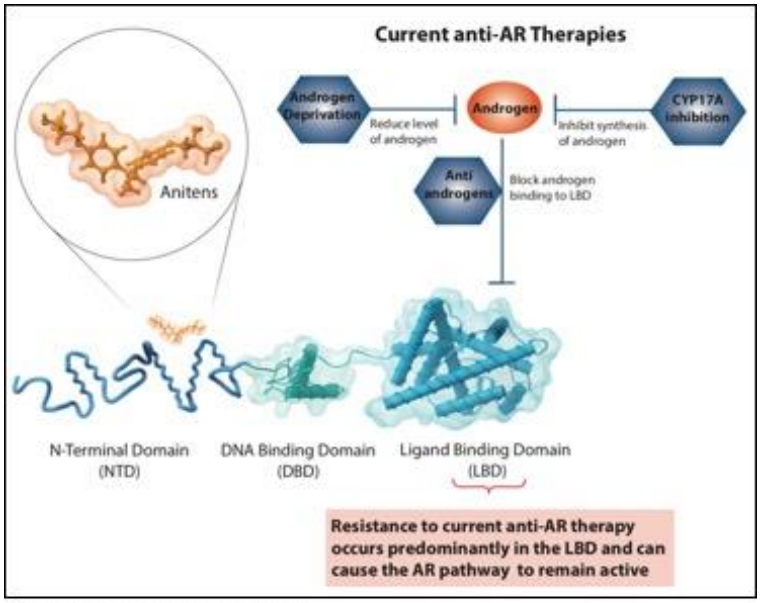
WHAT'S NEW

Business Update

New Preclinical Data Presented at AUA 2020

On May 15, 2020, ESSA Pharma Inc. (EPIX) announced new preclinical data was presented at the 2020 American Urological Association (AUA) Annual Meeting (the poster can be accessed here) for its lead clinical candidate EPI-7386, which is part of a novel class of compounds known as 'anitens' to treat prostate cancer in patients that are progressing on standard of care therapy. Anitens target the androgen receptor (AR), which is the main signaling mechanism driving the growth of prostate tumors, through binding to the N-terminal domain (NTD), which is unique compared to other available anti-androgen therapies that the target the ligand binding domain (LBD).

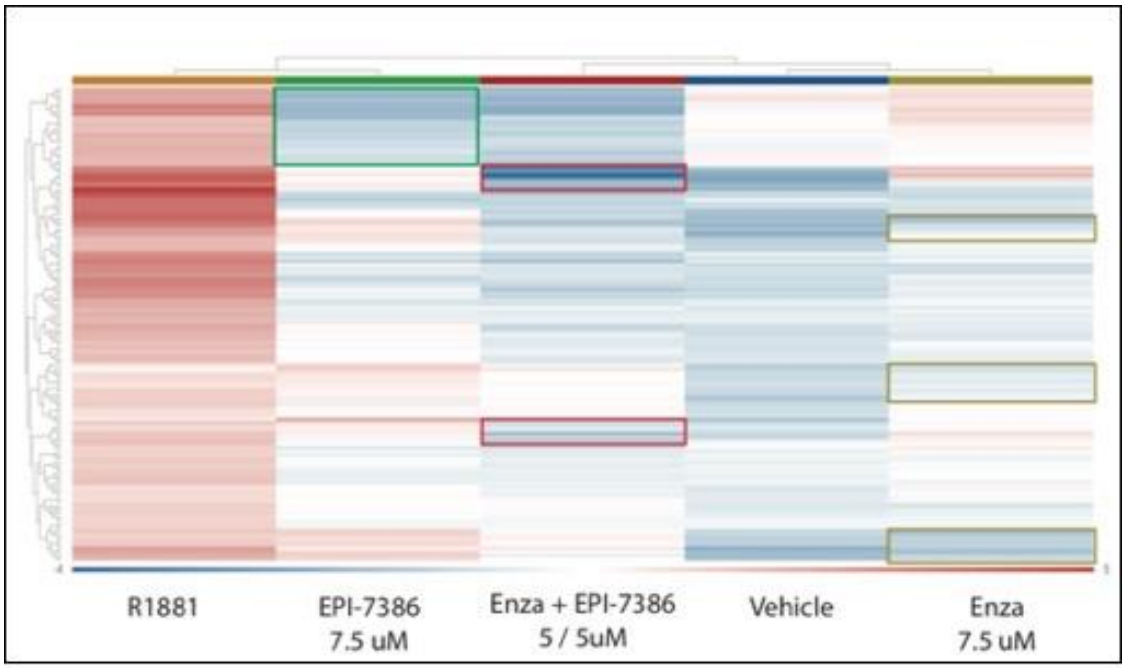
ESSA previously completed a Phase 1 trial with a first-generation aniten compound, EPI-506, that confirmed the safety and tolerability of this class of compounds. However, due to its short half-life and other negative pharmaceutical properties, the development of EPI-506 was discontinued while research continued on the development of next-generation anitens. This work led to the discovery of EPI-7386, a next-generation aniten that has a number of advantages compared to first-generation anitens. The following graphic shows where anitens bind on the AR compared to currently available anti-AR therapies, which fully differentiates anitens from other prostate cancer therapies that target the AR.



Source: Le Moigne *et al.*, 2020

The data presented at the 2020 AUA Annual Meeting built upon results previously presented by the company (see here for a discussion of the results presented at the 2020 ASCO Genitourinary Cancers Symposium). Additional data presented on EPI-7386 included gene expression analyses and toxicology studies evaluating the safety of the compound.

The following figure shows gene expression data in LNCaP cells, which is an androgen-sensitive human prostate adenocarcinoma cell line, in the presence of EPI-7386, enzalutamide, EPI-7386+enzalutamide, vehicle, or R1881 (methyltrienolone). R1881 is a synthetic androgen and is considered the "gold standard" AR agonist. The heat map shows the expression of genes that are >2-fold higher in the presence of R1881 for 24 hours compared to vehicle. EPI-7386 and enzalutamide down-regulate a number of those genes both as single treatments and as a combination.



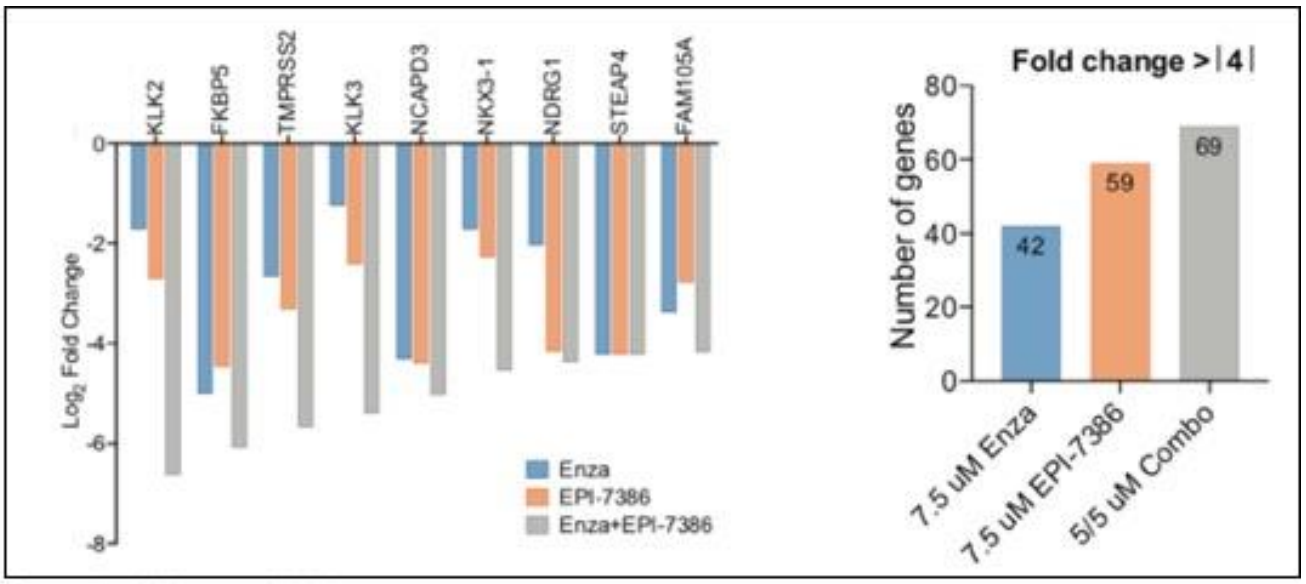
Source: Le Moigne *et al.*, 2020

The boxes in the figure above highlight groups of genes that are down-regulated specifically by each treatment group, with the pathways those genes are involved in shown in the following table. The most interesting aspect of this data is that while EPI-7386 has an impact on most of the R1881-induced genes, EPI-7386 appears to affect a similar but slightly different set of genes than enzalutamide. For example, the genes in the green box (EPI-7386 specific effects) are mostly focused on cell cycle phase transition and DNA replication initiation and are more highly inhibited with EPI-7386 than with enzalutamide. In addition, the combination of EPI-7386 and enzalutamide appears to have a greater effect than either compound alone, particularly in genes involved in androgen response.

R1881-activated genes	Pathway Implication	Gene
Co-downregulated by Enza and EPI (74)	HALLMARK_Androgen response ($p\ adj=3.25x10^{-70}$) GO_Reproduction ($p\ adj=3.1x10^{-10}$) GO_Regulation of Cell population Proliferation ($p\ adj=3.1x10^{-10}$)	
Strongly downregulated by EPI only(22)	GO_Cell Cycle Phase Transition ($p\ adj=2.22x10^{-16}$) GO_DNA Replication Initiation ($p\ adj=3.95x10^{-16}$)	ORC6, CDC45, MCM4, CCNA2, E2F1, NDRG1, CDC6, AKAP12, CCNE2, POLA2, HIST2H2AB, FANCD2, TYMS, CREB3L4, CDK2, BRCA1, ERCC6L, CAMKK2, PLK1, ORC1, UBE2C, HIST1H2BN
Strongly downregulated by Enza only (25)	HALLMARK_TNFa Signaling via NFkB ($p\ adj=3.82x10^{-7}$) HALLMARK_EMT ($p\ adj=38.21x10^{-4}$)	STK17B, PTPN21, SEC24D, ID2, SAT1, SLC16A6, KLF4, TNFAIP8, WIPI1, DNAJB9, HERPUD1, B4GALT1, CALU, ZBTB10, ITGAV, LMAN1, B2M, PGM3, GHR, ABHD3, ERRFI1, SNAI2, CENPN, STK39, HERC3, IQGAP2, ALDH1A3, UAP1
Strongly downregulated by Enza + EPI combo (11)	HALLMARK_Androgen Response ($p\ adj=3.82x10^{-7}$)	KLK3, NKX3-1, KLK2, TMPRSS2, GUCY1A3, ZBTB16, RRP9, HES6, KLK4, ENDOD1, ABHD2, SMAGP

Source: Le Moigne *et al.*, 2020

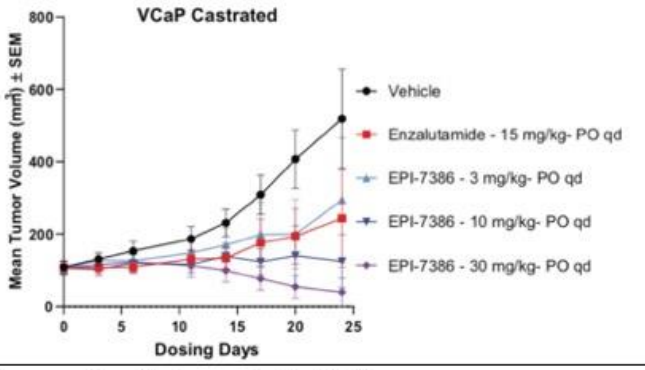
Looking at the gene expression data set a bit further, the following figure shows the fold decrease in expression for the nine most down regulated genes following combination treatment with enzalutamide and EPI-7386. A number of those genes are down-regulated to some degree by either enzalutamide or EPI-7386, however combining them together results in a much greater effect, in particular for KLK3 (prostate specific antigen, PSA). The number of genes that show a >4-fold change in expression is also greater in the combination arm compared with either enzalutamide or EPI-7386 used alone. These data support the company's plan to initiate combination therapy trials with EPI-7386 and enzalutamide (and/or apalutamide and/or darolutamide) in earlier line patients that are not yet resistant to 'lutamide' therapy. The gene expression data shows that combination therapy may result in a greater response rate in these patients, and if that were the case it would undoubtedly pique the interest of potential Big Pharma partners.



Source: Le Moigne *et al.*, 2020

An examination of toxicology data compared to efficacy data in mouse xenograft models shows that EPI-7386 is very well tolerated and we believe that the recommended Phase 2 dose is likely to be discovered fairly quickly in the upcoming Phase 1 clinical trial.

The following figure on the left shows the representative activity of EPI-7386 in a VCaP xenograft model, where 10 mg/kg EPI-7386 shows tumor growth inhibition while 30 mg/kg EPI-7386 shows tumor shrinkage. The table on the right shows representative pharmacokinetic (PK) data for different concentrations of EPI-7386 in different strains of mice.



Dose (mg/kg)	Mouse strain	Day of dosing	Cmax (ng/mL)	AUC0-last (ng·h/mL)
3	CD-1	1	6,610	87,200
10	CD-1	1	16,300	220,000
30	CD-1	1	45,300	534,000
30	Nude / SCID / SCID Beige / NOG	1	38,750	475,000
30	Nude / SCID / SCID Beige / NOG	7	31,000	282,000

Source: Le Moigne *et al.*, 2020

Considering the PK parameters above in regards to efficacy in the xenograft models, the toxicology data shows that there is likely to be a very wide margin for safety in dosing EPI-7386. The dog toxicology data in the following table shows that a dose that is well-tolerated and below the highest non-severe toxic dose (HNSTD) results in an AUC value of 1,350,000 ng*h/mL. Comparing this to the data above shows that an efficacious dose in mice had an AUC of 220,000 – 534,000 ng*h/mL, two- to five-fold lower than the HNSTD.

Male Beagle dog 28-days GLP Tox

Dose (mg/kg/day)	AUC0–24h D27 (ng·h/mL)	Major Findings	Conclusion
20	529,000	Well tolerated and non-adverse	NOAEL
50	1,350,000	Well tolerated and non-adverse	Below HNSTD
90/70	1,850,000	Adverse body weight and food consumption loss. No other significant clinical or anatomical pathology findings	HNSTD

NOAEL: No-observed -adverse-event level; HNSTD: Highest non-severe toxic dose. Repeat dose showed minimal accumulation between D1 and D27 . Anti-androgen effects observed on target organs.

Source: Le Moigne *et al.*, 2020

Lastly, the following table gives PK estimates for different doses of EPI-7386 in humans based on in vitro in vivo correlation. A dose of 200 mg (the recommended starting Phase 1 dose based on the toxicology data) is predicted to result in an AUC of 137,278 ng*hr/mL while a dose of 400 mg is estimated to result in an AUC of 274,556 ng*hr/mL, which is very close to the AUC for the efficacious dose in the mouse xenograft model and well below the HNSTD. This data gives us confidence that EPI-7386 will be safe and well tolerated and could lead to discovery of the recommended Phase 2 dose in a relatively short period of time based on a starting dose of 200 mg.

Dose (mg)	Cmax (ng/mL)	AUC0-24 (ng*hr/mL)
50	1,729	34,320
100	3,458	68,639
200	6,915	137,278
400	13,830	274,556
800	27,659	549,113

AUC and Cmax calculated at steady state

Source: Le Moigne *et al.*, 2020

To summarize:

- EPI-7386 shows efficacy in a mouse xenograft model with tumor growth inhibition at 10 mg/kg and tumor shrinkage at 30 mg/kg. These doses result in AUC values of 220,000 and 534,000 ng*hr/mL, respectively.

- Toxicology data shows that the HNSTD for rats is a dose that results in an AUC value of 2,350,000 ng*hr/mL and in dogs a dose that results in an AUC value of 1,850,000 ng*hr/mL. These values are approximately three- to four-fold lower than the AUC achieved for a dose of EPI-7386 that results in tumor shrinkage in a mouse xenograft model.

- Modeled human PK data shows that a dose of 200 mg (the recommended starting dose for the Phase 1 clinical trial based on the toxicology data) will result in an AUC of approximately 137,000 ng*hr/mL and a dose of 400 mg will result in an AUC of approximately 275,000 ng*hr/mL, which is very close to the AUC derived from a dose that results in tumor growth inhibition in a mouse xenograft model.

- Comparing the xenograft/PK/toxicology data leads us to believe that 1) EPI-7386 has a wide margin for safe dosing and 2) the recommended Phase 2 dose is likely to be determined rather quickly given how close the starting dose is to one that is predicted to show efficacy.

IND Cleared to Start Phase 1 Clinical Trial of EPI-7386

In April 2020, ESSA announced that the Investigational New Drug (IND) application received clearance from the FDA to initiate a Phase 1 clinical trial of EPI-7386 for the treatment of metastatic castration-resistant prostate cancer (mCRPC).

We anticipate the Phase 1 clinical trial enrolling approximately 18 patients who are resistant to second-generation anti-androgens therapies (e.g., enzalutamide) to evaluate the safety, pharmacokinetics, and maximum-tolerated dose of the compound in multiple-dose escalations. It will encompass a standard 3+3 trial design (three patients enrolled per dose cohort) with an estimated 10 patients being enrolled in the dose expansion cohort. The initial dose will be 200 mg, followed by 400 mg, 600 mg, 800 mg, and 1000 mg.

The primary objective of the dose escalation portion is to establish the safety and efficacy of EPI-7386 with the secondary objective being to determine the maximum tolerated dose and the recommended Phase 2 dose. In the dose expansion portion of the trial, the primary objective will be to further evaluate the safety, tolerability, and preliminary anti-tumor activity of the recommended Phase 2 dose.

The company is also planning to initiate a combination trial with EPI-7386 and a 'lutamide' (enzalutamide, apalutamide, or darolutamide) in mCRPC patients due to the robust preclinical data showing increased activity with combination therapy. We estimate that the company is fully financed to conduct all three trials (the dose escalation trial, the dose expansion trial, and the combination trial).

Valuation

We value ESSA using a probability adjusted discounted cash flow model that takes into account potential future revenues for EPI-7386. We model for ESSA to partner the asset and to receive a 15% royalty on net sales.

For EPI-7386, we estimate that the company will initiate a Phase 1 trial in 2020, a Phase 3 trial in 2023, and file for approval in 2025. While the opportunity for accelerated approval is a possibility, we are maintaining our more conservative timeline for now. However, given the recent approval of Rubraca® for the treatment of BRCA1/2-mutated mCRPC based on Phase 2 data from the TRITON2 trial in 62 patients with a BRCA1/2 mutation, the chance for accelerated approval could certainly be available with strong efficacy.

For the initial indication, which is patients with mCRPC who are no longer responding to anti-androgen therapy, we estimate there are approximately 30,000 in the U.S. and 80,000 in the E.U. who would be eligible for treatment based on the number of deaths attributed to prostate cancer each year. While this represents a potential billion-dollar opportunity on its own, we believe the much larger opportunity exists in combination therapy with earlier stage patients. We estimate there are approximately 160,000 patients who have either non-metastatic CRPC, metastatic hormone sensitive PC, or ADT-failing metastatic CRPC. When including these patients in our model we believe EPI-7386 could achieve peak sales of $4 billion worldwide. Using a 35% chance of approval along with a 13% discount rate leads to a net present value for EPI-7386 of $316 million. Combining the net present value of EPI-7386 with the company's current estimated cash balance and dividing by an estimated fully diluted share count of 38.2 million leads to a valuation of approximately $10.50 per share.

PROJECTED FINANCIALS

ESSA Pharma Inc.	FY2019 A	Q1FY20 A	Q2FY20 A	Q3FY20 E	Q4FY20 E	FY2020 E	FY2021 E	FY2022 E
EPI-7386	$0	$0	$0	$0	$0	$0	$0	$0
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-
Research & Development	$6.7	$2.6	$4.6	$2.0	$2.0	$11.2	$10.0	$12.0
Financing Costs	$0.6	$0.2	$0.1	$0.0	$0.0	$0.3	$0.0	$0.0
General & Administrative	$5.5	$2.1	$4.9	$1.4	$1.4	$9.8	$6.0	$7.0
Other (Income) Expense	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($12.8)	($4.9)	($9.6)	($3.4)	($3.4)	($21.3)	($16.0)	($19.0)
Operating Margin	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	$2.4	($0.0)	($0.2)	$0.0	$0.0	($0.2)	$0.0	$0.0
Pre-Tax Income	($10.4)	($4.9)	($9.4)	($3.4)	($3.4)	($21.6)	($16.0)	($19.0)
Income Taxes	$0.0	($0.3)	$0.0	$0.0	$0.0	($0.3)	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($10.4)**	**($4.6)**	**($9.4)**	**($3.4)**	**($3.4)**	**($21.3)**	**($16.0)**	**($19.0)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($1.24)**	**($0.22)**	**($0.45)**	**($0.16)**	**($0.16)**	**($1.03)**	**($0.53)**	**($0.54)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	8.4	20.8	20.8	20.8	20.8	20.8	30.0	35.0

Source: Zacks Investment Research, Inc. *David Bautz, PhD*

© Copyright 2019, Zacks Investment Research. All Rights Reserved.

HISTORICAL STOCK PRICE



© Copyright 2019, Zacks Investment Research. All Rights Reserved.

DISCLOSURES

The following disclosures relate to relationships between Zacks Small-Cap Research ("Zacks SCR"), a division of Zacks Investment Research ("ZIR"), and the issuers covered by the Zacks SCR Analysts in the Small-Cap Universe.

ANALYST DISCLOSURES

I, David Bautz, PhD, hereby certify that the view expressed in this research report accurately reflect my personal views about the subject securities and issuers. I also certify that no part of my compensation was, is, or will be, directly or indirectly, related to the recommendations or views expressed in this research report. I believe the information used for the creation of this report has been obtained from sources I considered to be reliable, but I can neither guarantee nor represent the completeness or accuracy of the information herewith. Such information and the opinions expressed are subject to change without notice.

INVESTMENT BANKING AND FEES FOR SERVICES

Zacks SCR does not provide investment banking services nor has it received compensation for investment banking services from the issuers of the securities covered in this report or article.
Zacks SCR has received compensation from the issuer directly, from an investment manager, or from an investor relations consulting firm engaged by the issuer for providing non-investment banking services to this issuer and expects to receive additional compensation for such non-investment banking services provided to this issuer. The non-investment banking services provided to the issuer includes the preparation of this report, investor relations services, investment software, financial database analysis, organization of non-deal road shows, and attendance fees for conferences sponsored or co-sponsored by Zacks SCR. The fees for these services vary on a per-client basis and are subject to the number and types of services contracted. Fees typically range between ten thousand and fifty thousand dollars per annum. Details of fees paid by this issuer are available upon request.

POLICY DISCLOSURES

This report provides an objective valuation of the issuer today and expected valuations of the issuer at various future dates based on applying standard investment valuation methodologies to the revenue and EPS forecasts made by the SCR Analyst of the issuer's business.
SCR Analysts are restricted from holding or trading securities in the issuers that they cover. ZIR and Zacks SCR do not make a market in any security followed by SCR nor do they act as dealers in these securities. Each Zacks SCR Analyst has full discretion over the valuation of the issuer included in this report based on his or her own due diligence. SCR Analysts are paid based on the number of companies they cover. SCR Analyst compensation is not, was not, nor will be, directly or indirectly, related to the specific valuations or views expressed in any report or article.

ADDITIONAL INFORMATION

Additional information is available upon request. Zacks SCR reports and articles are based on data obtained from sources that it believes to be reliable, but are not guaranteed to be accurate nor do they purport to be complete. Because of individual financial or investment objectives and/or financial circumstances, this report or article should not be construed as advice designed to meet the particular investment needs of any investor. Investing involves risk. Any opinions expressed by Zacks SCR Analysts are subject to change without notice. Reports or articles or tweets are not to be construed as an offer or solicitation of an offer to buy or sell the securities herein mentioned.

CANADIAN COVERAGE

This research report is a product of Zacks SCR and prepared by a research analyst who is employed by or is a consultant to Zacks SCR. The research analyst preparing the research report is resident outside of Canada, and is not an associated person of any Canadian registered adviser and/or dealer. Therefore, the analyst is not subject to supervision by a Canadian registered adviser and/or dealer, and is not required to satisfy the regulatory licensing requirements of any Canadian provincial securities regulators, the Investment Industry Regulatory Organization of Canada and is not required to otherwise comply with Canadian rules or regulations.