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Reviva Pharmaceuticals, Inc. (RVPH: NASDAQ)

Brilaroxazine Enthusiasm Abounds

Based on our DCF model and a 15% discount rate, Reviva is valued at approximately $16.00 per share. Our model applies a 50% probability of ultimate approval and commercialization for RP5063 for schizophrenia. The model includes contributions from the United States and rest of world.

Current Price (3/9/2023)	$4.65
Valuation	**$16.00**

OUTLOOK

Reviva is a research and development pharmaceutical company with two portfolio compounds targeting nine indications. The candidates address multiple related mental disorders, rare diseases & other categories of unmet need. Reviva's lead indication in schizophrenia with brilaroxazine (RP5063) began a Phase III trial in 2022. Complementary Phase II work with RP5063 in ADHD and PAH may also begin.

Brilaroxazine is a novel, multimodal serotonin, dopamine & nicotinic receptors modulator with an improved efficacy & side effect profile compared with other antipsychotics. The drug class is established with over $10 billion in revenues. Unmet need persists in the category, related to efficacy, side effects & drug regimen compliance. Brilaroxazine's improved profile is expected to carve material share from the existing market and expand into untreated patients. Secondary candidate, RP1208, is in preclinical studies for depression and obesity.

After agency review in the US and other jurisdictions, we anticipate approval to be granted by the FDA in 2025 followed by other territories. Our valuation assumes commercialization in the US and rest of world in 2025 and 2026 respectively.

SUMMARY DATA

52-Week High	**$6.10**
52-Week Low	**$0.53**
One-Year Return (%)	**166**
Beta	**0.1**
Average Daily Volume (sh)	**143,598**
Shares Outstanding (mil)	**20.4**
Market Capitalization ($mil)	**94.9**
Short Interest Ratio (days)	**7.7**
Institutional Ownership (%)	**6.4**
Insider Ownership (%)	**26.9**
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 2022 Estimate	**N/A**
P/E using 2023 Estimate	**N/A**
Zacks Rank	**N/A**

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

ZACKS ESTIMATES

Revenue
(In millions of US$)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2021	$0.0 A	$0.0 A	$0.0 A	$0.0 A	$0.0 A
2022	$0.0 A	$0.0 A	$0.0 A	$0.0 E	$0.0 E
2023					$0.0 E
2024					$0.0 E

Earnings per Share

	Q1	Q2	Q3	Q4	Year
2021	-$0.10 A	-$0.12 A	-$0.12 A	-$0.19 A	-$0.58 A
2022	-$0.40 A	-$0.29 A	-$0.18 A	-$0.27 E	-$1.17 E
2023					-$0.73 E
2024					-$0.54 E

WHAT'S NEW

March Update

Since our previous report that was submitted on the occasion of Reviva Pharmaceutical Holdings, Inc's (NASDAQ: RVPH) third quarter results, the company has reported the award of new patents, completed brilaroxazine drug-drug interaction studies and an updated stakeholders on the Phase III RECOVER trial. CEO Laxminarayan Bhat, PhD, has also participated in investor events and interviews discussing active and future programs.

Dr. Bhat Interview

Exhibit I – Dr. Bhat Discusses Brilaroxazine Product Profile[1]

Interviews with Reviva's CEO, Dr. Laxminarayan Bhat:

- Reviva: Next Generation Blockbuster
- Reviva's Clinical and Regulatory Timelines
- Reviva: More Than Schizophrenia
- Reviva's Brilaroxazine Addresses Antipsychotics' Biggest Hurdles
- Fireside Chat: Reviva's RP1208 & Thoughts on Peers

RP1208 Composition of Matter Patent

Reviva holds two compounds in its portfolio of assets: lead candidate brilaroxazine and secondary candidate RP1208. The latter of these is a triple reuptake inhibitor in preclinical development for depression and obesity. Both of these assets are fully owned by Reviva and the claim on their intellectual property was recently strengthened with the grant of a composition of matter patent in Canada. The patent (CA2858837C) protects the composition of novel phenylcycloalkylmethylamine derivatives (PDs) and methods of preparing them. The invention also provides methods of using PDs for the pharmacological treatment of obesity, depression and obesity related co-morbid indications.

[1] Screenshot from March 2023 Interview with Dr. Bhat.

Parallel Registrational Studies

One of Reviva's required parallel registrational studies is for drug-drug interaction (DDI), which is especially important in schizophrenia patients. Antipsychotic medications are the primary class of drugs used to treat schizophrenia, which work by blocking dopamine receptor activity in the brain. However, not all antipsychotic medications work equally well for all patients and some individuals may experience significant side effects. As a result, healthcare providers may need to prescribe a combination of different antipsychotics or other medications, such as mood stabilizers or antidepressants, to achieve the best results for their patients resulting in multiple drug regimens.

Reviva announced positive safety data from its DDI study investigating the potential effect of CYP3A4 enzyme on brilaroxazine in healthy subjects. Management believes the data reinforce brilaroxazine's potential advantage over other treatments for patients taking multiple drugs who are at higher risk of experiencing adverse drug interactions or discontinuation of their medications due to those interactions. Following FDA guidelines, the DDI clinical study was designed to evaluate the drug interaction effect of a strong CYP3A4 inhibitor or inducer when co-administered with brilaroxazine. The CYP3A4 inhibitor, itraconazole, slightly increased brilaroxazine C_{max}, AUC_{last} and AUC_{inf} by 6%, 16% and 13%, respectively, in 11 healthy volunteers. Similarly, a strong CYP3A4 inducer, phenytoin, in 16 healthy volunteers decreased the drug's C_{max}, AUC_{last} and AUC_{inf} by 33%, 56% and 53%, respectively. The DDI study found no clinically significant interaction when combined with a CYP3A4 inhibitor.

Individuals with schizophrenia may have other medical conditions in addition to their mental health condition, and as a result, they may need to take medications for other disorders. Some common medical conditions that may occur alongside schizophrenia include high blood pressure, diabetes and obesity.

Additionally, some medications used to treat schizophrenia can cause side effects or have interactions with other drugs. This requires the use of yet other therapies to manage these issues. For example, some antipsychotic medications can cause weight gain or increase the risk of developing diabetes and individuals taking antipsychotics may need other drugs to manage these coincident disorders.

It is important for providers to consider the potential interactions between medications when treating individuals with schizophrenia, as well as monitor for any side effects or adverse reactions to the medications. To provide the necessary data to support these decisions, sponsors must run DDI studies. According to Reviva's research approximately 50% of prescribed drugs and over 25% of antipsychotics currently on the market are known to cause drug interactions with CYP3A4 inhibitors. Brilaroxazine, specifically, is metabolized by CYP3A4 and CYP2D6. In an unpublished study which will be submitted to the FDA in the NDA, brilaroxazine produced an increase in the area under the curve (AUC)[2] in the pharmacokinetic analysis of 15% with a CYP3A4 inhibitor and a 54% AUC decrease with a CYP3A4 inducer. This compares favorably with other commonly prescribed antipsychotics.

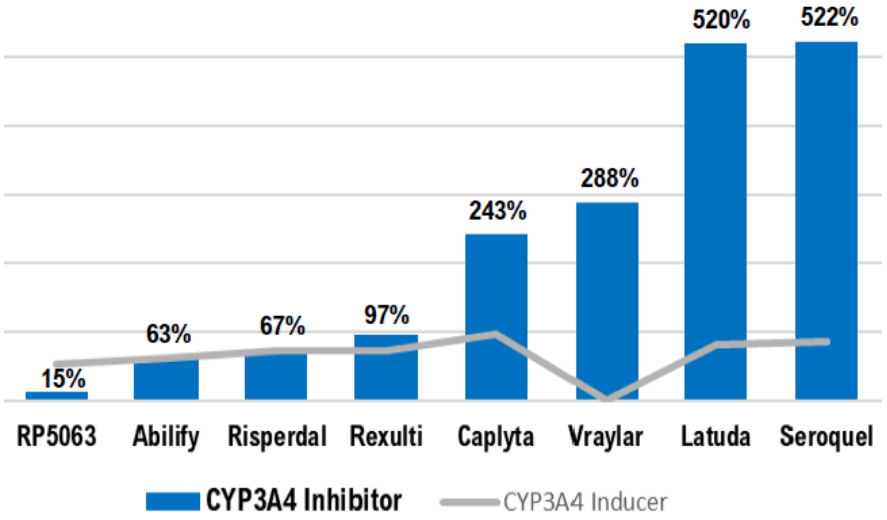
Exhibit II – Drug-Drug Interaction Comparison of Leading Antipsychotics with Brilaroxazine[3]

	Antipsychotic	AUC Increase with CYP3A4 Inhibitor	AUC Decrease with CYP3A4 Inducer
1	**Brilaroxazine[1] RP5063**	**15%**	**54%**
2	Abilify[2]	63%	61%
3	Rexulti[3]	97%	73%
4	Vraylar[4]	288%	Not evaluated
5	Seroquel[5]	522%	87%
6	Risperdal[6]	67%	72%
7	Zyprexa[7]	Not evaluated (CYP1A2)*[8]	Not evaluated (CYP1A2)
8	Latuda[9]	520%	82%
9	Caplyta[10]	243%	98%

[2] AUC represents the total amount of drug in the bloodstream over a given period of time after a single dose or multiple doses of the drug.
[3] Source: Reviva Corporate Presentation February 2023.

CYP3A4 is a key enzyme responsible for metabolizing a wide range of drugs in the liver. CYP3A4 inhibitors are drugs or compounds that inhibit the activity of this enzyme, which can lead to slower metabolism and clearance of other drugs that are substrates for CYP3A4. As a result, the AUC of these drugs may increase when taken together with a CYP3A4 inhibitor. A minimal change in AUC increase is preferred as it allows for blood plasma levels of the drug to be closer to targeted levels. CYP3A4 inducers are drugs or compounds that increase the activity of this enzyme, which can lead to faster metabolism and clearance of other drugs that are substrates for CYP3A4. As a result, the AUC of these drugs may decrease when taken together with a CYP3A4 inducer. Minimizing the decrease in AUC is desired as it attenuates the reduction in drug levels in plasma from therapeutically efficacious levels.

Exhibit III – Change in Plasma Drug Concentration (AUC) [4]



Itraconazole

In addition to its use as an antifungal medication, itraconazole is sometimes used as a CYP3A4 inhibitor to enhance the effects of other medications. It has been used to increase the blood levels of certain chemotherapy drugs, which can improve their effectiveness against cancer. It is also used in drug-drug interaction studies to evaluate its effects on other medications. Itraconazole is a potent inhibitor of the cytochrome P450 enzyme CYP3A4, which is involved in the metabolism of many drugs. As a result, itraconazole can affect the metabolism and elimination of other medications that are also metabolized by CYP3A4.

When itraconazole is co-administered with drugs that are metabolized by CYP3A4, it can increase the blood levels of those drugs by inhibiting their metabolism. This can cause an increased risk of side effects and toxicities associated with those drugs. Therefore, it's important to monitor patients closely when itraconazole is used in combination with other medications that are metabolized by CYP3A4.

Phenytoin

Phenytoin is a medication that is primarily used to treat seizures and epilepsy. It is also known to induce the activity of several cytochrome P450 enzymes, including CYP3A4. As a CYP3A4 inducer, phenytoin can increase the metabolism and elimination of other medications that are also metabolized by CYP3A4. This can result in lower blood levels of those drugs, potentially reducing their effectiveness.

Phenytoin is a useful tool in DDI studies as it can induce the cytochrome P450 enzyme system. By evaluating its effects on other medications, researchers can better understand how different drugs interact with each other and how to optimize patient drug therapy.

Examples of medications that may experience reduced effectiveness by the CYP3A4-inducing effects of phenytoin:

- Oral contraceptives: increased risk of pregnancy;
- Anticoagulants: increase metabolism, which reduces blood levels of medications such as warfarin;
- Antidepressants: causes lower blood levels of medications such as fluoxetine;
- Antipsychotics: causes lower blood levels of medicines such as clozapine.

[4] Source: Reviva Corporate Presentation February 2023.

CYP3A4 (Cytochrome P450 3A4)
CYP3A4 (cytochrome P450 3A4) is a member of the cytochrome P450 family of enzymes that is primarily found in the liver, but can also be found in other tissues such as the intestine. CYP3A4 plays an important role in the metabolism and elimination of a many drugs, toxins, and endogenous substances, including steroids and bile acids.

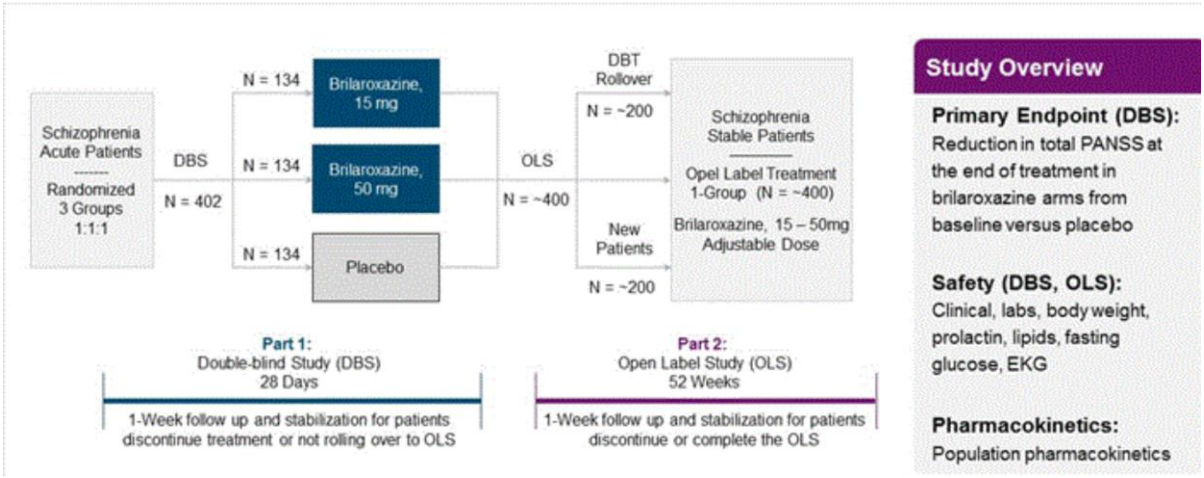
CYP3A4 metabolizes drugs via oxidation, a process that facilitates their elimination from the body. However, the activity of CYP3A4 can also be influenced by various factors such as genetics, age, diet, and other medications. Certain drugs can inhibit or induce the activity of CYP3A4, which can affect the metabolism and elimination of other drugs that are also metabolized by CYP3A4.

Because CYP3A4 is involved in the metabolism of many drugs, it is one of the most important drug-metabolizing enzymes in the human body. Understanding the effects of CYP3A4 on drug metabolism is crucial in determining appropriate dosages, preventing drug interactions and avoiding adverse drug reactions.

RECOVER Phase III Trial

Reviva announced on January 4, 2023 that it had enrolled 40% of the targeted 400 patients by year end 2022. It expects to deliver top-line data from the Phase III trial around mid-year 2023. By early March we anticipate that Reviva's Phase III trial, designated RECOVER (NCT05184335) is over half enrolled. As illustrated in the exhibit below, the trial consists of a four-week efficacy study followed by a one-year safety extension.

Exhibit IV - RECOVER Trial Design[5]



Brilaroxazine will be administered at fixed doses of 15 mg or 50 mg once daily. The study will assess both dose levels over 28 days in the double-blind phase in acute schizophrenia for a total of three arms, randomized 1:1:1, including placebo. In the 52-week open-label extension in stable schizophrenia, subjects will be dosed at 15 mg, 30 mg or 50 mg. Primary outcome measures are the change in total Positive and Negative Syndrome Scale (PANSS) scores from baseline over the 28-day evaluation period. Secondary outcome measures include antipsychotic efficacy using a variety of scales and subscales. In the Phase II REFRESH study, 15 mg was the best performing, with the 50 mg arm a close second in terms of efficacy.

Inclusion of the 50 mg dose arm will allow therapeutic insight, both in terms of efficacy and safety, in higher doses in a population almost double the size, and will give Reviva an additional opportunity to meet primary endpoints. The open-label cohort will comprise both subjects who participated in the double-blind phase and new (*de novo*) subjects. With a 52-week open-label extension following the 28-day double-blind phase, the trial is expected in total to last 56 weeks. As demonstrated in earlier studies, brilaroxazine represents class-leading tolerability in terms of side-effects, a significant deterrent to treatment adherence in the patient population suffering from schizophrenia.

[5] Reviva 2021 10-K

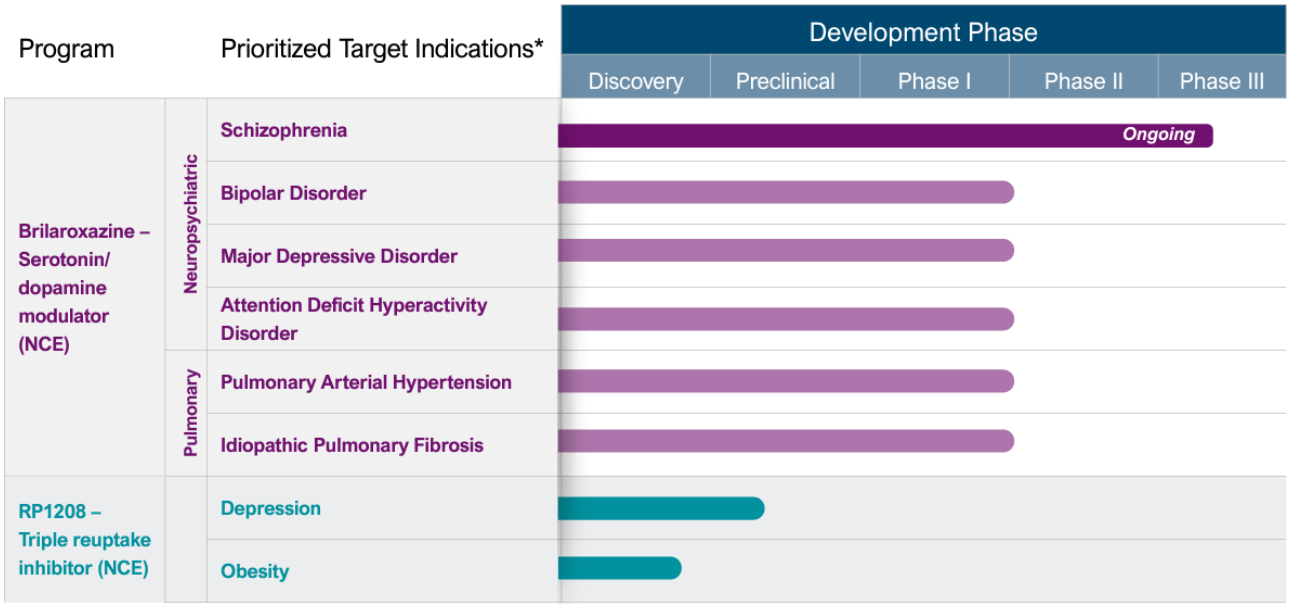
Milestones

Preparation for Phase II trials for brilaroxazine in additional indications is underway with regulatory work expected in the next quarters followed by launch, pending funding. We provide additional detail on recent and anticipated achievements below:

- RECOVER sites in India open – 4Q:22
- Completion of DDI study – December 2022
- Developing Phase II protocols for studies in PAH and ADHD – 2023
- Estimated last patient enrolled in RECOVER – March 2023
- Estimated last patient last visit in RECOVER – April 2023
- Phase III schizophrenia RECOVER topline data – July 2023
- Launch further Phase II studies in new indications – 2023
- Second Phase III confirmatory trial – 4Q:23
- Pursue strategic partnerships to support pipeline development – 2023
- Brilaroxazine NDA submission – Late 2024/Early 2025

Company Pipeline

Exhibit V – Reviva Pipeline[6]



Summary

Reviva has continued to make progress with its brilaroxazine program for schizophrenia, and we esimate that trial enrollment is over half complete. We discuss some of the finer points of Reviva's progress with CEO Laxminarayan Bhat, PhD in a series of interviews included above. As the year progresses, further work will be conducted on the logistics and planning for the second Phase III trial in coming months in preparation for its future start.

Reviva should have sufficient cash to make it through to the end of RECOVER and beyond. We could also see additional funds contributed from warrant exercises due to the upward move in the stock. Non-dilutive funding from partnerships and grants are also being considered. Reviva's lead candidate, brilaroxazine, represents class-leading tolerability in an indication where side effects deter treatment adherence. We maintain our valuation of $16.00 per share.

[6] Source: Reviva Pharmaceuticals October 2022 Corporate Presentation.

PROJECTED FINANCIALS

Reviva Pharmaceutical Holdings Inc. - Income Statement[7]

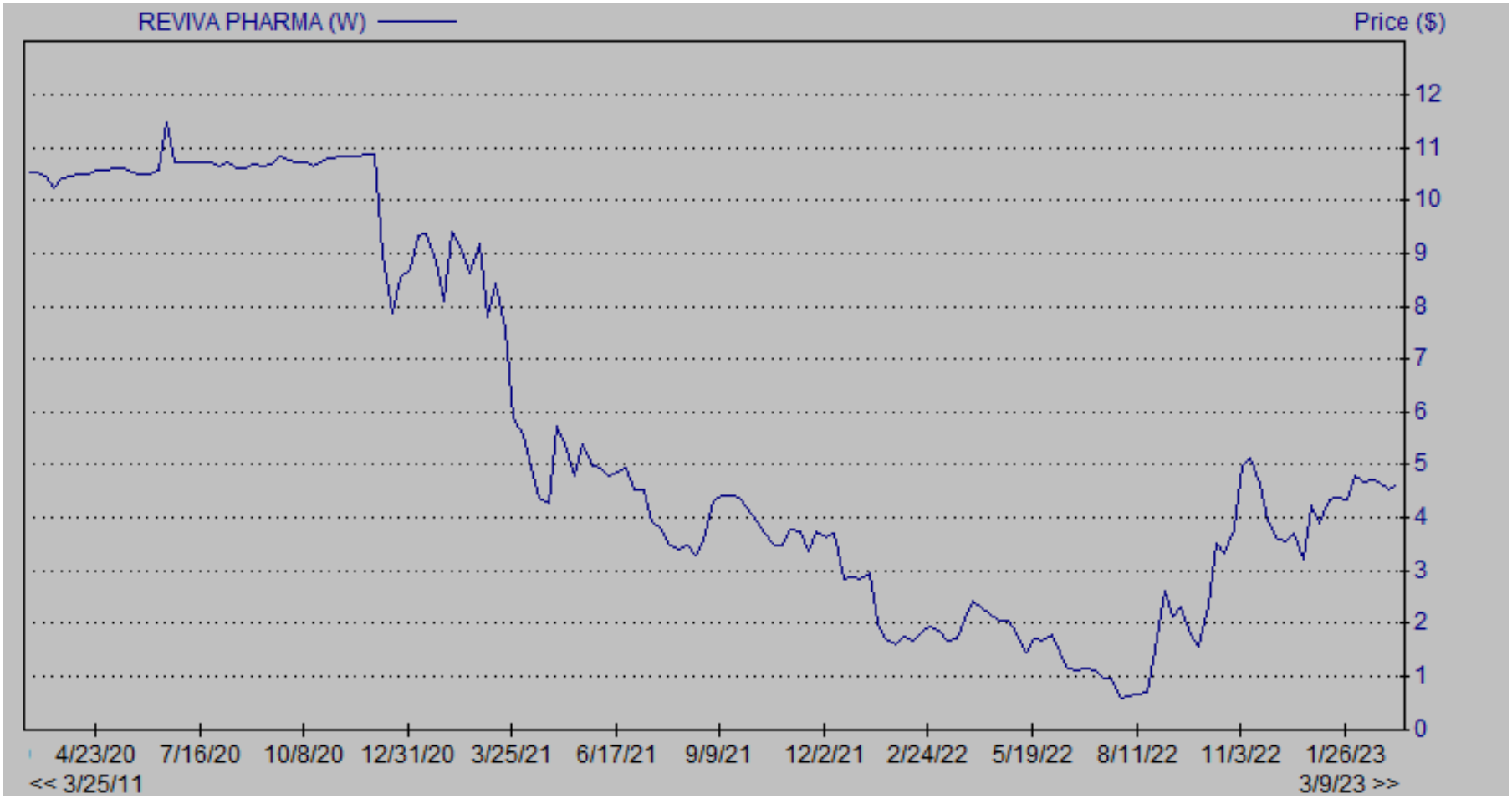
Reviva Pharmaceuticals	2021 A	Q1 A	Q2 A	Q3 A	Q4 E	2022 E	2023 E	2024 E
Total Revenues ($US ,000)	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth								
Research & Development	$4,852	$5,830	$4,514	$2,306	$4,200	$16,850	$9,250	$7,000
General & Administrative	$5,253	$1,620	$1,005	$1,257	$1,425	$5,307	$5,850	$6,100
Income from operations	($10,105)	($7,450)	($5,519)	($3,563)	($5,625)	($22,158)	($15,100)	($13,100)
Operating Margin								
Other Income (Expense)	$1,589	$89	$186	$50	$0	($422)	($441)	($410)
Pre-Tax Income	($8,516)	($7,361)	($5,334)	($3,513)	($5,625)	($22,580)	($15,541)	($13,510)
Provision for Income Tax	$6	$4	$7	$2	$0	$12		
Tax Rate	*0.0%*					*0.0%*		
Net Income	**($8,522)**	**($7,365)**	**($5,341)**	**($3,515)**	**($5,625)**	**($22,592)**	**($15,541)**	**($13,510)**
Net Margin	*# DIV/0!*	*# DIV/0!*	*# DIV/0!*	*# DIV/0!*	*# DIV/0!*	*# DIV/0!*	*# DIV/0!*	*# DIV/0!*
Reported EPS	**($0.58)**	**($0.40)**	**($0.29)**	**($0.18)**	**($0.27)**	**($1.17)**	**($0.73)**	**($0.54)**
YOY Growth	*-53%*	*287.9%*	*131.5%*	*47.9%*	*38.0%*	*103%*	*-0.37520117*	*-0.26108359*
Basic Shares Outstanding	14,791	18,467	18,467	19,270	21,000	19,301	21,250	25,000

Source: Company Filing // Zacks Investment Research, Inc. Estimates

[7] Historical financial statement information presents data as originally reported.

HISTORICAL STOCK PRICE

Reviva Pharmaceutical Holdings, Inc. – Share Price Chart[8]



[8] Source: Zacks Research System

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