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June 1, 2018
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BiondVax Pharmaceuticals, Ltd. (BVXV-NASDAQ)

BVXV: Increased Media Coverage for M-001 Ahead of Phase 3 Clinical Trial…

Based on our probability adjusted DCF model that takes into account potential future revenues from M-001 as a universal flu vaccine, BVXV is valued at $37/share. This model is highly dependent upon continued clinical success of M-001 and will be adjusted accordingly based upon future clinical results.

Current Price (06/01/18)	$6.45
Valuation	**$37.00**

OUTLOOK

BiondVax Pharmaceuticals, Ltd. is a biopharmaceutical company developing a universal influenza vaccine (M-001) designed to protect individuals from all strains of influenza. The company is currently in the planning stages for a global Phase 3 program for M-001 as a standalone universal influenza vaccine. The first Phase 3 trial is expected to take place in Eastern Europe and should begin in the second half of 2018.

BiondVax recently highlighted a number of stories in the media about the potential for a universal influenza vaccine and M-001. These types of stories are a very positive development for the company as it heads into the start of the Phase 3 trial this Fall.

SUMMARY DATA

52-Week High	**$10.42**
52-Week Low	**$4.73**
One-Year Return (%)	**-11.95**
Beta	**1.20**
Average Daily Volume (sh)	**6,982**
Shares Outstanding (mil)	**7**
Market Capitalization ($mil)	**$42**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**7**
Insider Ownership (%)	**6**
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 2018 Estimate	**N/A**
P/E using 2019 Estimate	**N/A**

Risk Level	**Above Avg.**
Type of Stock	**Small-Blend**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	0.0 A	0.0 A	0.0 A	0.0 A	0.0 A
2018	0.0 A	0.0 E	0.0 E	0.0 E	0.0 E
2019					0.0 E
2020					0.0 E

Earnings Per Share

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2017	-$0.02 A	-$0.02 A	$0.00 A	-$0.00 A	-$0.03 A
2018	-$0.02 A	-$0.01 E	-$0.01 E	-$0.01 E	-$0.04 E
2019					-$0.04 E
2020					-$0.04 E

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WHAT'S NEW

Business Update

Phase 3 Study of M-001 Set to Commence in 2H18

BiondVax Pharmaceuticals,Ltd. (BVXV) is a biopharmaceutical company developing a universal influenza vaccine (M-001) designed to protect individuals from all strains of influenza. The company's strategy for commercializing M-001 involves testing it in a pivotal Phase 3 program as a standalone influenza vaccine to assess its clinical efficacy. The first Phase 3 trial will be conducted in Europe and the company has received feedback about the trial design and approval to initiate it from the European Medicines Agency (EMA). The EMA also stated that "a single pivotal efficacy trial that provides a robust demonstration of efficacy against laboratory-proven influenza like illness (ILI) could suffice for an approval". In addition, the company is working to align the Phase 3 plan with FDA requirements.

The trial is being conducted in Eastern Europe due to the fact that there are either no recommendations for getting the yearly influenza vaccine or it is an out of pocket expense, thus influenza vaccination rates are low and it is much easier to enroll sufficient numbers of subjects who have not been previously immunized with the yearly influenza vaccine. Recently, the company announced the selection of a Contract Research Organization (CRO) to conduct the trial.

The general outline for the Phase 3 trial is shown below. The company is planning to enroll approximately 9,630 patients and will focus on patients over the age of 50. Approximately half of those subjects will be enrolled prior to the first influenza season. The trial is designed such that a certain overall rate of influenza infection is required for the trial to be properly powered. Thus, unblinding of the data following the first influenza season will be dictated by the overall rate of infection (i.e., how severe of an influenza season it is). If it is a mild influenza season, then additional subjects will likely need to be enrolled in Season 2 and the subjects from Season 1 will be followed as well. This process will continue until a sufficient number of influenza infections occur in the entire cohort, potentially into Season 3. Subjects from Season 1 will be followed up regardless of when the study is unblinded to determine long-term effectiveness of M-001.

Trial Design	Season 1			Season 2	Season 3 (optional)
	Day 1	Day 21	Day 202	Follow up	Follow up
Experimental	1mg M-001	1mg M-001	Safety, PCR and culture on any ILI (flu season)	PCR and culture on any ILI (flu season)	PCR and culture on any ILI (flu season)
Control	Placebo	Placebo			

Source: BiondVax Pharmaceuticals, Ltd.

The primary outcome of the trial will be safety and clinical efficacy of M-001, defined as a reduction in illness rate and severity. We anticipate the trial initiating in Fall 2018 before the start of the 2018/2019 influenza season. A U.S. based contract manufacturing organization (CMO) will likely produce the first batch of M-001 for use in the first cohort of patients, while BiondVax will produce the subsequent batches in the new manufacturing facility.

Increasing Media Coverage for M-001

In May 2018, BiondVax highlighted a number of media publications that discussed the quest for a universal influenza vaccine and/or M-001. Below we highlight a few of these and note that the increased media coverage is a positive development for the company.

A New Push for a Universal Flu Vaccine – Scientific American. This article gives a broad overview of the difficulties in developing a universal influenza vaccine and highlights M-001 as a promising candidate. The article mainly focuses on the Phase 2 clinical trial of M-001 being conducted by NIAID, which is important as that trial is the first of M-001 in the U.S. In addition, the fact that the trial is being conducted by the NIAID (a division of the NIH) lends instant credibility to the story.

A Checkup for the Flu Vaccine – Nature Medicine. This article mainly discusses the difficulties in developing a universal influenza vaccine. It also discusses the Flu Vaccine Act, which is requesting $1 billion over five years for the NIH to fund development of a universal influenza vaccine. M-001 is also mentioned briefly in its ability to elicit a T-cell response, which is a differentiating feature compared to the current seasonal influenza vaccine.

NIAID-Sponsored Trial of a Universal Influenza Vaccine Begins – NIAID. This article discusses the initiation of the Phase 2 clinical trial of M-001 testing its ability to elicit a broadly protective immune response when used in conjunction with the seasonal influenza vaccine. The study is enrolling up to 120 healthy volunteers between the ages of 18 and 49 who will be randomly assigned to receive either two doses of M-001 or placebo spaced 22 days apart followed approximately 172 days later by the seasonal influenza vaccine. BiondVax is supplying sufficient quantities of M-001 for the trial while NIAID is funding all other aspects of the trial. The study is designed to evaluate the cell mediated immunity induced by M-001 as well as its ability to enhance the immunogenicity of the current seasonal influenza vaccine. Safety and immunogenicity will be assessed between M-001 and placebo treated groups. This trial is particularly important as it signifies that M-001 is on the NIH's radar, which would be a prerequisite in order to receive funding should it become available under the Flu Vaccine Act.

Financial Update

On May 29, 2018, BiondVax announced financial results for the first quarter of 2018. As expected, the company did not report any revenues during the quarter or year. The company had a net loss of $4.0 million for the first quarter of 2018, which was comprised of $3.3 million in R&D expenses and $0.3 million in G&A expenses.

As of March 31, 2018, BiondVax had cash and cash equivalents of approximately $15.8 million and no debt. Total cash burn for the first quarter of 2018 was approximately $4.6 million, which was mainly directed toward preparing for the upcoming Phase 3 clinical trial and anticipated expenses for construction of the company's manufacturing facility. As a reminder, in June 2017 BiondVax entered into a $22 million (€20 million) loan agreement with the European Investment Bank (EIB). The non-dilutive financing agreement is structured as a 0% fixed interest rate loan. The funds will be made available in three tranches, up to 12, 24, and 36 months following the date of the agreement. Amounts between €4-6 million will be disbursed in tranches 1 and 2, with the remainder of the funds available in tranche 3. Once drawn, each tranche must be paid back on the five-year anniversary from the date of drawdown. The end result of this financing arrangement for BiondVax is that the company now has up to half of the funding necessary for the Phase 3 program for M-001We estimate that BiondVax currently has enough capital to fund operations into 2019.

Background on M-001

BiondVax is developing the M-001 vaccine, a synthetic peptide-based protein that targets both existing and future seasonal and pandemic strains of the influenza virus. The vaccine targets conserved regions of Type A and B influenza viruses such that M-001 could be considered a "universal" influenza vaccine, capable of offering immunological protection against all strains of the influenza virus.

M-001 is composed of nine peptides that are believed to be common to most known influenza strains in existence, in part because these peptides seem to be critical for the virus' ability to infect a host cell. They are derived from hemagglutinin (HA), matrix 1 (M1) and nucleoprotein (NP) viral proteins and are arranged as triplicates into a single recombinant protein easily manufactured in bacteria. HA is an antigenic glycoprotein found on the surface of influenza viruses and is also the main constituent for a number of seasonal influenza vaccines. However, the peptides from HA in M-001 are derived from the inner parts of the protein where little to no variability between strains exists. M1 is a matrix protein that forms a layer under the patches of the viral cell membrane that contain HA, NA, and M2 proteins, and is responsible for mediating the encapsulation of RNA-nucleoprotein complexes into the membrane envelope (Sha *et al*., 1997). NP is a structural protein that encapsidates the viral RNA inside the virus. The sequence of each of the peptides is shown below, along with the order in which the peptides are arranged in the full-length recombinant protein.

Peptide	Amino Acids Sequence
Hemagglutinin (HA) epitope 1	PKYVKQNTLKLAT
Hemagglutinin (HA) epitope 2	SKAYSNCYPYDVPDYASL
Hemagglutinin (HA) epitope 3	WLTGKNGLYP
Hemagglutinin (HA) epitope 4	WTGVTQN
Hemagglutinin (HA) epitope 5	PAKLLKERGFFGAIAGFLE
Nucleoprotein (NP) epitope 6	FWRGENGRKTRSAYERMCNILKGK
Nucleoprotein (NP) epitope 7	SAAFEDLRVLSFIRGY
Nucleoprotein (NP) epitope 8	ELRSRYWAIRTRSG
Matrix (M) epitope 9	SLLTEVETYVP

(HA epitope 1) - (HA epitope 2) - (M1 epitope 9) - (HA epitope 3) - (HA epitope 4) - (NP epitope 6) - (HA epitope 5) - (NP epitope 7) - (NP epitope 8).

Source: Atsmon *et al*., 2012

The peptides were selected based upon their ability to elicit either a B- or T-cell immune response and each of them has the ability to bind to a wide array of human leukocyte antigen (HLA) proteins (both Class I and Class II), which are responsible for presenting peptides to the immune system. Some may question the use of peptides from proteins located inside the virus, however there is a strong rationale for their use. It has long been known that a mild influenza infection in animals provides protection against a subsequent, more severe challenge with a virus harboring different HA and NA (Yetter *et al*., 1980). This effect appears to be mediated by both CD4+ and CD8+ T-cells that recognize conserved regions on viral proteins (Furuya *et al*., 2010). The CD4+ T-cells that are specific for conserved internal viral antigens also potentiate antibody responses to the HA of subsequently encountered viruses (Scherle *et al*., 1986). The end result is that immunizing with conserved internal viral antigens results in an increased immunological response to infection following subsequent exposure to influenza viruses.

Previous Clinical Trial Results

M-001 had been tested in 698 participants through six different clinical trials, with the details presented in the following chart. In each of the trials, the vaccine was shown to be safe and able to induce a robust immune response.

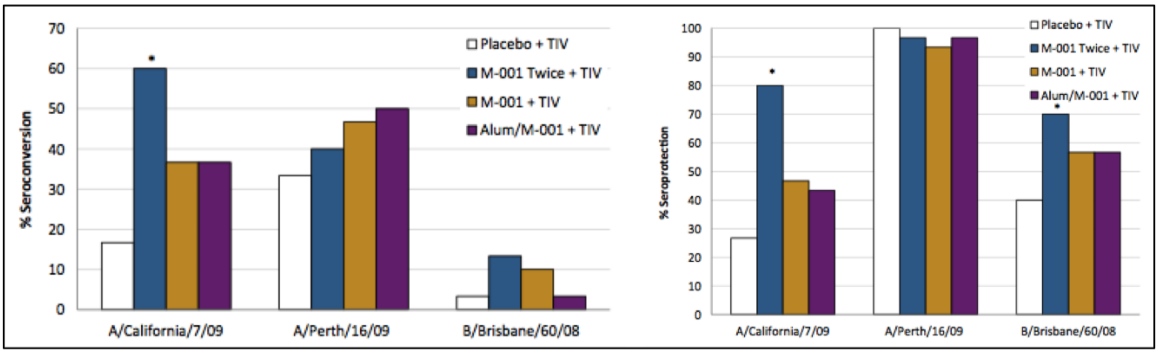
Phase	Trial	Year	Population (age)	Total Participants	Status	Results
1/2	BVX-002	2009	Younger Adults (18-49)	63	Completed	M-001 was well tolerated and a cellular (CMI) and humoral (priming effect) immune response was observed
1/2	BVX-003	2010	Older Adults (55-75)	60	Completed	
2	BVX-004	2011	Younger Adults (18-49)	200	Completed	
2	BVX-005	2012	Elderly (65+)	120	Completed	
2	BVX-006	2015	Older Adults (50-65)	36	Completed	
2b	BVX-007*	2015-16	EU Adults (18-60)	219	Completed	

Source: BiondVax Pharmaceuticals Ltd.

BVX-002 (Atsmon *et al*., 2012): This was a single-center, randomized, placebo controlled, single blind first-in-human study to examine the safety and immunological response to M-001 in healthy adults age 18-49. For safety purposes, three subjects were dosed once with 0.125 mg of M-001 and monitored for 7-9 days before the rest of the patients were administered the planned doses. There were four dosing cohorts, and within each cohort subjects were randomized in a 2:1 fashion to receive either 0.25 mg or 0.5 mg M-001 (n=10) or placebo (n=5), with or without adjuvant. The results showed that M-001 was well tolerated with only mild and moderate adverse events (AEs), with no significant difference between vaccine and placebo recipients for AEs. A robust humoral (antibodies to M-001) and cellular (PBMC proliferation to viral peptides) immune response was noted for participants immunized with M-001, and while there were greater humoral responses in patients immunized with M-001 plus adjuvant, there did not appear to be a difference in cellular response between subjects dosed with adjuvant and those without.

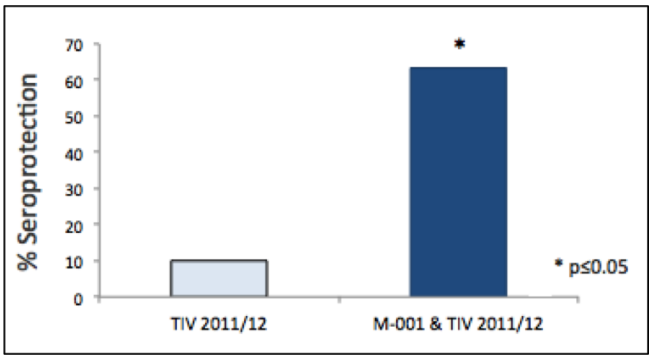
BVX-005 (Atsmon *et al*., 2014): This was a two-center, randomized, placebo controlled study in a total of 120 elderly volunteers (age 65+). The subjects were randomized 1:1:1:1 into four parallel groups to receive either 1) two sequential non-adjuvanted 0.5 mg M-001, or 2) a single non-adjuvanted 0.5 mg M-001, or 3) a single adjuvanted IM

injection of 0.5 mg M-001, or 4) one placebo injection. All participants subsequently received the seasonal trivalent influenza vaccine (TIV) three weeks following the last M-001 or placebo injection. The primary outcome measures were safety, tolerability, and tolerance of M-001 with secondary outcomes being humoral and cellular immune responses. The results showed that priming with M-001 enhanced seroconversion towards all three strains in that season's influenza vaccine (denoted on the y-axis in the figure below). The following figure shows the percentage of patients that tested positive for seroconversion (defined as a mean fold increase in anti-HA antibody levels of ≥ four-fold from levels detected in sera collected on day 0, and reaching a level of ≥1:40 post-immunization) and seroprotection (defined as the number of participants per cohort expressing anti-HA antibody levels of ≥1:40 post-immunization). Addition of an adjuvant did not appear to offer any additional immunostimulatory effect.



Source: Atsmon *et al*., 2014

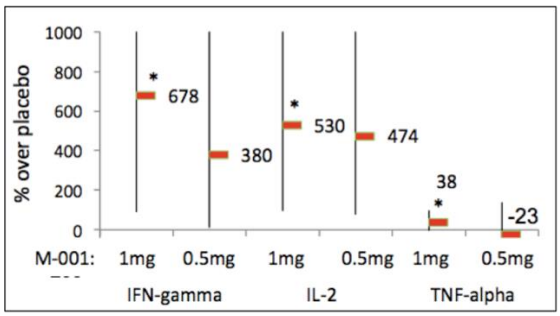
In 2015, a new 'Swiss' epidemic influenza strain (H3N2: A/Switzerland/9715293/13) emerged that did not exist in 2011, which was when the BVX-005 trial took place and the participants in the trial were immunized with M-001. Blood serum samples from the participants in the BVX-005 trial were exposed to the 'Swiss' influenza strain, with results showing that greater than 60% of the M-001 vaccinated group had seroprotection against this new Swiss strain, compared to only 10% of those immunized with just the seasonal vaccine. This suggests that M-001 may offer a broader, long-lasting immune response not just to strains currently in existence, but to future strains that do not even exist yet!



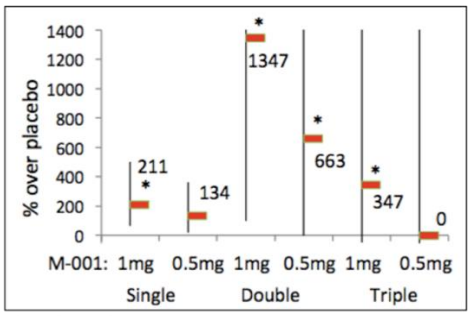
Source: BiondVax Pharmaceuticals, Ltd.

BVX-007: In 2017, BiondVax announced results from the company's Phase 2b clinical trial of M-001. The trial, which was funded through a grant from the European Union and was conducted in conjunction with the European UNISEC Consortium, enrolled a total of 219 participants aged 18 to 60 years. Each participant received two injections of 0.5 mg M-001, 1.0 mg M-001, or placebo prior to a partial dose of avian H5N1 pandemic vaccine.

The trial hit both primary endpoints for safety and immunological response. To test for immunological response, T cell activation was measured in *in vitro* assays through the release of the cytokines interleukin (IL)-2, interferon (INF)-γ, and tumor necrosis factor (TNF)-α. The following figure on the left shows that statistically significant T cell activation was found in participants that received 1.0 mg M-001 when compared to the placebo group. The following figure on the right shows that the there was a significant increase in T cells that expressed two cytokines, which have been shown to be functionally superior to single-cytokine producing T cells (Kannanganat *et al*., 2007).



Source: BiondVax Pharmaceuticals Ltd.



Source: BiondVax Pharmaceuticals Ltd.

The study's secondary endpoint evaluated antibody response to avian H5N1 pandemic vaccination. In one of the four H5N1 strains tested there was a statistically significant increase in antibody response in those receiving M-001.

Conclusion and Valuation

BiondVax continues to steadily execute on its business plan and it's nice to see the increased media coverage of M-001 as the company moves toward initiation of the pivotal Phase 3 program. While not required to move M-001 into the Phase 3 program, the Phase 2 trial being conducted by the NIH will provide additional scientific insight into M-001's mechanism of action as well as providing additional safety data in another cohort of subjects. It also marks the first trial of M-001 in the U.S., and the fact that it is being sponsored by the NIH lends significant credibility to the story.

As a stand-alone universal vaccine, we model for M-001 to have peak market share of 25% in the U.S., which leads to peak revenues of approximately $750 million, and peak revenues of approximately $300 million overseas. We believe peak revenue forecasts for >$1 billion are justified based upon the clear advantages that M-001 has over the seasonal influenza vaccines, particularly in regard to efficacy without any limitations brought about by whichever influenza strain happens to be circulating. With a 16% discount rate and a 50% probability of approval, we value M-001 as a standalone vaccine at approximately $229 million.

Our model also includes the stockpiling of M-001 as a pandemic influenza vaccine. The critical workforce in the U.S. is approximately 15% of the population (20 million people), and 1/3rd of the stockpile is replaced annually (given a shelf-life of three years). At $12 per dose that represents a $240 million annual opportunity. We apply a 16% discount rate and a 50% probability of approval to arrive at a net present value for M-001 as a primer for a pandemic vaccine of $100 million.

Combining the net present value for M-001 as a stockpiled and standalone vaccine along with the company's current cash position and expected operating burn of leads to a valuation of $37 per share.

PROJECTED FINANCIALS

BiondVax Therapeutics, Ltd.	2017 A	Q1 A	Q2 E	Q3 E	Q4 E	2018 E	2019 E	2020 E
M-001 (Elderly Primer)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth		-	-	-	-			
M-001 (Pandemic Primer)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth		-	-	-	-			
M-001 (Universal Vaccine)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth		-	-	-	-			
Grants & Collaborative Revenue	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth		-	-	-	-			
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth		-	-	-	-			
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin		-	-	-	-			
Research & Development	$5.4	$3.3	$1.8	$2.0	$2.5	$9.6	$10.0	$12.0
General & Administrative	$1.4	$0.3	$0.4	$0.5	$0.5	$1.7	$1.9	$2.0
Other Expenses	$0	$0	$0	$0	$0	$0	$0	$0
Operating Income	($6.8)	($3.6)	($2.2)	($2.5)	($3.0)	($11.3)	($11.9)	($14.0)
Operating Margin		-	-	-	-			
Non-Operating Expenses (Net)	($3.1)	($0.4)	$0.0	$0.0	$0.0	($0.4)	$0.0	$0.0
Pre-Tax Income	($10.0)	($4.0)	($2.2)	($2.5)	($3.0)	($11.7)	($11.9)	($14.0)
Income Taxes Paid	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($10.0)**	**($4.0)**	**($2.2)**	**($2.5)**	**($3.0)**	**($11.7)**	**($11.9)**	**($14.0)**
Net Margin		-	-	-	-			
Reported EPS	**($0.05)**	**($0.02)**	**($0.01)**	**($0.01)**	**($0.01)**	**($0.04)**	**($0.04)**	**($0.04)**
Basic ADS Outstanding	5.0	6.5	6.6	6.6	6.7	6.6	7.5	8.0

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

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