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BiondVax Pharmaceuticals, Ltd. (BVXV-NASDAQ)

BVXV: Update on Phase 3 Clinical Trial of Universal Influenza Vaccine…

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 (04/17/19)	$6.79
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 conducting a Phase 3 clinical trial to assess the safety and efficacy of M-001. The trial is taking place in Eastern Europe and the company has completed enrolling the first cohort of 4,094 patients. The second cohort of at least 6,000 patients will be enrolled prior to the 2019/2020 influenza season. (The DSMB confirmed safety in the first cohort). Topline results will be available in the second half of 2020.

SUMMARY DATA

52-Week High	**$7.00**
52-Week Low	**$3.97**
One-Year Return (%)	**1.95**
Beta	**1.18**
Average Daily Volume (sh)	**13,794**
Shares Outstanding (mil)	**7**
Market Capitalization ($mil)	**$44**
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-Growth**
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 A	0.0 A	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	-$0.03 A	-$0.00 A	-$0.01 E	-$0.05 E
2019					-$0.04 E
2020					-$0.04 E

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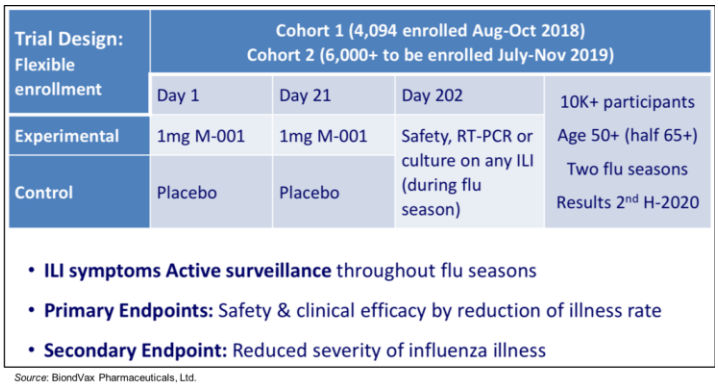
WHAT'S NEW

Business Update

Update on Phase 3 Clinical Trial of M-001

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 is being conducted in Europe following 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".

The company completed enrollment for the first season of the Phase 3 clinical trial in October 2018. A total of 4,094 participants were randomized 1:1 to receive either M-001 or placebo. The trial protocol includes options for flexible enrollment, in part to account for the chance of a particularly strong or weak flu season in the trial's first year. The initial plan was to monitor Cohort One individuals for two influenza seasons in the hope that there would be enough flu cases to show sufficiently strong statistical significance to claim that one injection of M-001 protects for two influenza seasons. Since the 2018/19 flu season appears to have been relatively weak, thereby reducing the likelihood of attaining sufficient flu cases to achieve statistical significance for showing two-year coverage, the company has decided to follow Cohort One participants through Season One, and divert the remaining resources towards recruiting additional Cohort Two participants. Thus, the second cohort of participants will involve more than 6,000 individuals to ensure the study is properly powered. This will be accomplished by increasing the number of countries (from four to seven) and clinical sites (from 54 to ~85) participating in the trial. An overview of the trial is below.



Source: BiondVax Pharmaceuticals, Ltd.

Topline results will be available in the second half of 2020, at which time the company will have data on >10,000 individuals to determine if M-001 is effective in reducing influenza illness against all naturally encountered influenza strains for one influenza season. We anticipate that additional trials aimed at extending the indication to more than one year are likely once M-001 reaches the market.

Phase 2 Study Fully Enrolled

On Mar. 21, 2019, BiondVax announced that the last participant has completed their final visit in a Phase 2 clinical trial of M-001 being conducted by the Vaccine Treatment and Evaluation Units, which is being sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), a part of the National Institutes of Health (NIH). The trial enrolled 120 participants between the ages of 18-49 at three centers in the U.S. Each participant received two doses of M-001 in the Spring and then a dose of the seasonal quadrivalent influenza vaccine in the Fall. The primary objectives of the trial are to assess the safety of M-001 and the T cell responses to M-001 component peptides. Secondary objectives of the trial include assessing serum antibody responses to the seasonal influenza vaccine target viruses. We anticipate data from the study at the end of 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

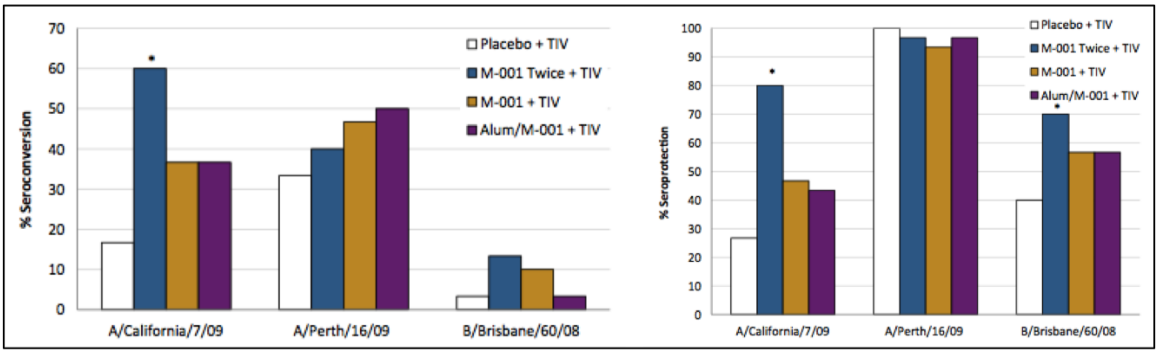
M-001 had been tested in 698 participants through six different clinical trials, with the details presented in the following chart. In each of the trials, the vaccine was shown to be safe and able to induce a robust immune response.

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.

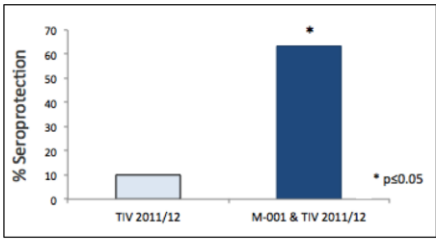
BVX-002 (Atsmon *et al*., 2012): This was a single-center, randomized, placebo controlled, single blind first-in-human study to examine the safety and immunological response to M-001 in healthy adults age 18-49. For safety purposes, three subjects were dosed once with 0.125 mg of M-001 and monitored 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

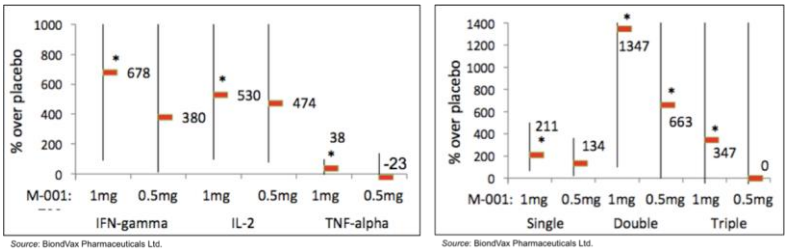
In 2015, a new 'Swiss' epidemic influenza strain (H3N2: A/Switzerland/9715293/13) emerged that did not exist in 2011, which was when the BVX-005 trial took place and the participants in the trial were immunized with M-001. Blood serum samples from the participants in the BVX-005 trial were exposed to 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).



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.

Valuation

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 A	Q3 A	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	$7.9	$1.2	$1.2	$13.6	$10.0	$12.0
General & Administrative	$1.4	$0.3	$0.4	$0.4	$0.5	$1.5	$1.9	$2.0
Other Expenses	$0	$0	$0	$0	$0	$0	$0	$0
Operating Income	($6.8)	($3.6)	($8.3)	($1.6)	($1.7)	($15.2)	($11.9)	($14.0)
Operating Margin		-	-	-	-			
Non-Operating Expenses (Net)	($3.1)	($0.4)	$1.0	$1.4	$0.0	$2.0	$0.0	$0.0
Pre-Tax Income	($10.0)	($4.0)	($7.3)	($0.2)	($1.7)	($13.2)	($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)**	**($7.3)**	**($0.2)**	**($1.7)**	**($13.2)**	**($11.9)**	**($14.0)**
Net Margin		-	-	-	-			
Reported EPS	**($0.05)**	**($0.02)**	**($0.03)**	**($0.00)**	**($0.01)**	**($0.05)**	**($0.04)**	**($0.04)**
Basic Shares Outstanding	201.0	261.4	261.4	261.4	267.0	262.8	300.0	320.0
Basic ADS Outstanding	5.0	6.5	6.5	6.5	6.7	6.6	7.5	8.0

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

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