EDISON

BiondVax Pharmaceuticals

Initiation of coverage

Most advanced universal influenza vaccine

Pharma & biotech

BiondVax with its epitope-based multimeric vaccine candidate M-001 is among the leaders in the development of the universal influenza vaccine worldwide. In previous clinical trials M-001 was shown to be consistently safe, immuno-genic and demonstrated synergy with conventional flu vaccines. The readout from the ongoing European Phase II study is imminent, while the initiation of the last Phase IIb study funded by the US National Institutes of Health (NIH), with results likely in H217/H118, will pave the way for partnering and the Phase III programme. We initiate coverage with a valuation of NIS269m ($71m).

Year end	Revenue (NISm)	PBT* (NISm)	EPS* (NIS)	DPS (NIS)	P/E (x)	Yield (%)
12/14	0.0	(7.8)	(0.14)	0.0	N/A	N/A
12/15	0.0	(10.2)	(0.10)	0.0	N/A	N/A
12/16e	0.0	(10.7)	(0.08)	0.0	N/A	N/A
12/17e	0.0	(10.8)	(0.08)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

Seeking multi-strain, multi-year flu protection

One of the main drawbacks of conventional influenza vaccination is historically low effectiveness, which, according to the US Centers for Disease Control and Prevention (CDC), averaged approximately 40% during the flu seasons from 2004 to 2016 and results partly from a mismatch between circulating influenza strains and those used to manufacture the seasonal vaccine. BiondVax aims to develop a vaccine that would provide multi-strain, multi-year protection against seasonal and pandemic viruses, broad protection for as long as possible.

Data consistent on M-001's immunogenicity

M-001 has so far been tested in two Phase I/II and three Phase II trials involving 479 participants in total. M-001 elicited immunogenicity to multiple flu virus strains and activated both humoral and cellular immune responses, as opposed to mainly strain-specific humoral arm stimulation with conventional seasonal flu vaccines. A synergistic effect was observed when using M-001 in conjunction with the conventional flu vaccine, which allows positioning BiondVax's vaccine candidate as a primer to any seasonal or pandemic vaccines. While this could be the fastest way to the market, the ultimate vision is to develop a standalone influenza vaccine with the goal of replacing the current strain-specific flu vaccines.

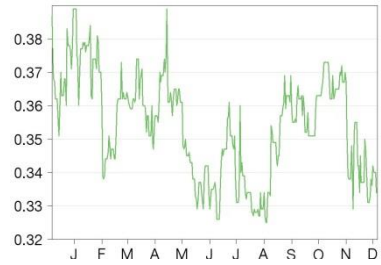
Valuation: NIS269m ($71m) or NIS2.0/sh ($21.0/ADR)

We initiate coverage of BiondVax with a valuation of NIS269m ($71m) or NIS2.0/share ($21.0/ADR), based on risk-adjusted NPV analysis and including NIS28.6m ($7.5m) net cash estimated at end-2016. We include two indications with M-001 as a primer for pandemic and seasonal vaccines, while standalone universal vaccine represents the upside. The imminent readout from the European Phase II study is the near-term share price driver, while the initiation of the last Phase II study (with results likely in H217/H118) will pave the way for partnering and the Phase III programme.

8 December 2016

Price	**NIS0.33**
Market cap	**NIS45m**
*Priced at 6 December 2016	
	NIS3.79/US$
Net cash at end Q316	NIS29.7m ($8.0m)
Shares in issue (does not include 116m outstanding options and warrants); ADR/shares 1:40	135.1m
Free float	95%
Code	BVXV
Primary exchange	TASE
Secondary exchange	NASDAQ

Share price performance



%	1m	3m	12m
Abs	(1.2)	(5.9)	(10.5)
Rel (local)	(4.9)	(5.2)	(4.5)
52-week high/low	NIS0.39	NIS0.33	

Business description

BiondVax is developing a potentially universal influenza vaccine and the lead candidate M-001 could be positioned as a primer for seasonal or pandemic vaccines or as a standalone influenza vaccine. So far M-001 has been tested in two Phase I/II and three Phase II trials and consistently demonstrated immunogenicity to multiple virus strains.

Next events

Results from Phase II with UNISEC in Europe	Q416/Q117
Start of enrolment in Phase II with NIH in the US	Q416/Q117

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Edison profile page

Investment summary

Company description: Most advanced universal flu jab

BiondVax, an Israel-based clinical-stage biopharmaceutical company, is developing a potentially universal influenza vaccine. With its peptide-based technology, which uses a combination of conserved and common epitopes from influenza virus proteins, BiondVax aims to develop a vaccine that would elicit multi-strain protection against seasonal and pandemic viruses. BiondVax's lead candidate M-001 could be a primer for seasonal or pandemic vaccines and the ultimate vision is to extend M-001's indication as a standalone influenza vaccine. So far M-001 has been tested in two Phase I/II and three Phase II trials involving 479 participants in total; the trials explored different regimens of vaccination and consistently demonstrated a good safety profile and immunogenicity to multiple virus strains and the ability to activate both humoral and cellular immune response, as opposed to mainly humoral arm stimulation with conventional seasonal flu vaccines. The final two Phase II studies are ongoing, while the efficacy of M-001 will be established in a Phase III trial, which could start in 2018. BiondVax trades on the Tel Aviv stock exchange. In May 2015 it listed its shares on Nasdaq, raising $9.5m. In November 2016, BiondVax registered a shelf prospectus with the US SEC for shares that could potentially bring in up to $150m; however, the company has not provided any fund-raising plans for the near future.

Valuation: NIS269m ($71m) or NIS2.0/sh ($21.0/ADR)

We value BiondVax based on risk-adjusted NPV analysis using a 12.5% discount rate and including NIS28.6m net cash estimated at end 2016. This corresponds to NIS269m ($71m) or NIS2.0/sh ($21.0/ADR). We have included two of the three indications envisioned by BiondVax, namely a primer for pandemic vaccines and a primer for seasonal vaccination for populations at risk, which are likely the fastest way to the market. We assume a partnership deal ahead of the Phase III study. The visibility of the deal should increase after the end of Phase II meeting, likely in H217 or H118, with the FDA prior to Phase III. If we include c 116m outstanding options and warrants, the relative valuation on a fully-diluted basis would be NIS1.1/share ($11.3/ADR).

Financials: Lean operations with cash reach to 2019

BiondVax is debt-free and we estimate cash and cash equivalents (cash, cash equivalents and short- and long-term marketable securities) of NIS28.6m at the end of 2016 compared to NIS37.5m at end-2015. BiondVax has a low operating cash burn (H116 R&D costs of NIS3.5m) as its partners UNISEC consortium in Europe and the National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, are funding the majority of the costs associated with the ongoing Phase II studies. BiondVax indicated that the cash burn is around $250k per month, which implies cash reach to 2019 assuming a similar level of activities.

Sensitivities: Typical mid-stage R&D risks apply

BiondVax is subject to the usual risks associated with R&D, including clinical development failures, regulatory risks, competition, partnering setbacks and financing and commercial risks. The biggest near-term sensitivities are related to the outcomes of the currently ongoing Phase II trial with M-001 in Europe (BVX-007) and the other Phase II (BVX-008) to be initiated in the US. Subsequent to this, obtaining a strong partner willing to invest in costly Phase III studies will be crucial for a clear commercialisation strategy. In parallel, the company is actively seeking sources for non-dilutive funding such as regional, royalty-bearing, sub-licensing and distribution agreements as well as major grants. So far, M-001 has consistently demonstrated a good safety profile and immunogenicity in clinical trials, but a large-scale Phase III trial will be needed to see whether this translates into clinical benefit in terms of protection against flu.

Outlook: Two Phase II trials with first readout soon

BiondVax's technology, in-licensed from Yeda Research and Development (Weizmann Institute of Science), is based on peptide technology, which uses a combination of conserved and common epitopes from influenza virus proteins. The company's lead candidate M-001 is in advanced Phase II stage and targets three indications: **primer to pandemic vaccine**, **primer to seasonal vaccine for population at risk** (eg the elderly) and ultimately **a standalone vaccine**.

High disease burden and low influenza vaccine effectiveness

In the US, seasonal flu causes around 23,000 deaths a year, mainly in the elderly, and 200,000 hospitalisations (CDC). Worldwide there are estimated to be 3-5 million severe cases annually resulting in 250,000-500,000 deaths (WHO). Children under two years, those aged 65 and over and the chronically ill are most at risk. For example, around 90% of seasonal flu related deaths occur in elderly people, as influenza worsens outcomes or existing chronic conditions (CDC). Molinari et al estimated that in the US the economic impact of seasonal influenza was $10.4bn in direct medical costs alone, with a significantly larger burden due to lost lives, earnings and productivity of $87.1bn.[1]

Current influenza vaccines are solely strain specific. Conventional 'subunit' vaccines are derived from surface proteins of three or four inactivated virus strains and rely predominantly on triggering antibody responses to the hemagglutinin protein. Live attenuated vaccines (eg Medimmune's FluMist) also contain 3-4 A/B strains. According to the CDC, the average overall adjusted vaccine effectiveness for influenza seasons in the general population has been approximately 40% over 2004-2016, partly due to the antigenic drift of influenza virus strains ('strain mismatch'), while the variation was significant over the same 2004-2016 from as low as 10% (2004) to as high as 60% (2010). Despite increasing vaccination rates, effectiveness is even lower in the elderly due to immunosenescence. There is a clear need for a more reliable vaccine that is both more immunoprotective and with coverage against a wider range of flu strains for the entire population and in particular for the elderly.

Exhibit 1: Basics of influenza virus

Influenza virus classification	Types: A, B and C. Influenza A viruses are subtyped according to their surface antigens (glycoproteins): hemagglutinin (HA, 18 serotypes) and neuraminidase (NA, 11 serotypes), eg H1N1. Influenza B viruses are separated into two lineages (Yamagata and Victoria), but are not subtyped.[2] Virus A has been the cause of all flu pandemics in humans, while virus A and B cause seasonal epidemics[3]. Influenza C infections cause mild respiratory illnesses.
Virus mutation	The viral RNA genome spontaneously mutates, resulting in gradual changes in the seasonal viruses known as antigenic *drift*. Since the new serotype is still somewhat similar to the prior one a large percentage of the people will still be immune. Larger genetic changes, called antigenic *shift*, is caused by re-assortment of the genome segments and occurs particularly in the hemagglutinin protein of influenza A viruses. This can create a pandemic with uncontrolled spreading throughout the population.
Pandemics are the result of antigenic shift	Only type A viruses cause pandemics as they have a reservoir in animals (birds, swine, bats). Genetic mixing between viruses of human and animal origin occasionally leads to a viable influenza A virus strain to which humans have little or no immunity. A recent example was the 2009 outbreak of H1N1 of swine origin ('swine flu'). Type A H5N1 and H7N9 (avian) is currently causing the greatest pandemic concern. Highly pathogenic H5N6 and H5N8 are other two avian flu type A viruses that are spreading across Europe and Asia through multiple bird species with the latest H5N6 outbreak in poultry farms reported in South Korea this month.
Seasonal flu	At any one time there is a mix of influenza viruses circulating in the human population. For the 2016-17 season vaccines are recommended to contain influenza strains A(H3N2), A(H1N1)pdm09 (2009 swine flu pandemic) and one or two B virus lineages (depending on whether the vaccine is trivalent or quadrivalent).
Vaccine strain selection	It takes around six months to produce the most widely used, egg-based influenza vaccines. Therefore, based on circulating virus samples, the World Health Organisation (WHO) annually predicts which seasonal A and B strains will likely dominate the next season. Vaccine manufacturers produce a new three-strain (trivalent, TIV) or four-strain (quadrivalent, QIV) influenza vaccine accordingly. However, antigenic drift/shift during the months between selection (in March) and vaccine distribution (September-November) can result in a mismatch between the strains in the vaccine and those circulating in the population. In this case the vaccine may not provide adequate protection.

Source: Edison Investment Research

1 N. Molinari. The annual impact of seasonal influenza in the US: Measuring disease burden and costs. Volume 25, Issue 27, 28 June 2007, Pages 5086–5096.

2 Prevention and Control of Seasonal Influenza with Vaccines. CDC, Recommendations and Reports / August 26, 2016 / 65(5); 1–54.

3 Q. M. Sheikh. Towards the knowledge-based design of universal influenza epitope ensemble vaccines. Bioinformatics, 32(21), 2016, 3233–3239.

Development strategy and route to market

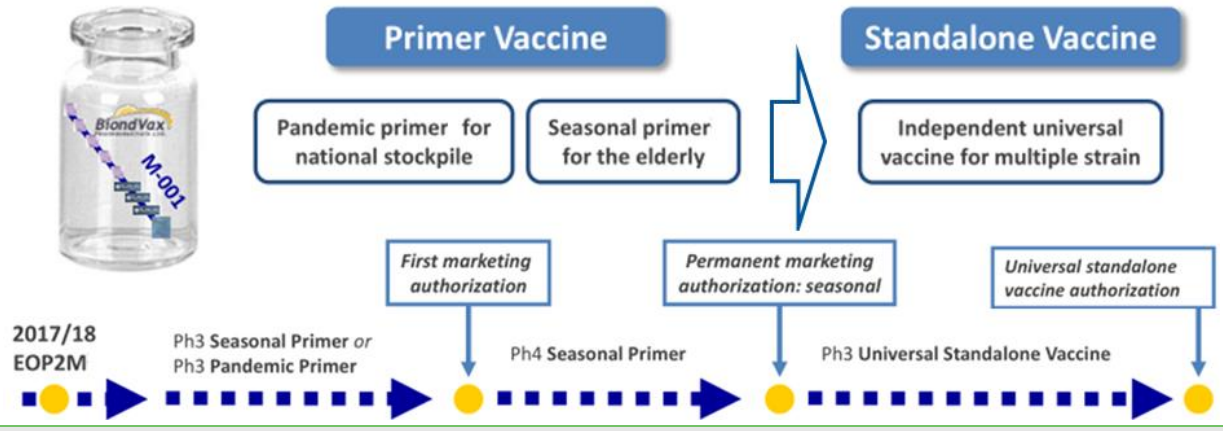
BiondVax is planning to commercialise the M-001 universal vaccine in two ways for three indications (Exhibit 2):

- As a primer vaccine to be used before any conventional HA-based flu vaccine. Two indications will be targeted: 1) **primer to seasonal vaccine for population at risk (ie elderly)**, and 2) **primer to pandemic vaccine for national stockpile**.
- As a **standalone vaccine** for multiple influenza strains.

Seasonal vaccines often fail to protect from flu infection due to the mismatch of the forecasted and prevailing virus strains, but also because of possible low efficacy even if there is a match. This situation implies that an effective universal vaccine would be relevant as a primer to a seasonal vaccine at least in specific populations at risk. The second initial indication is priming before pandemic flu vaccine is ready, which could take months to produce. In this instance M-001 would be bought for the national stockpiles by governments. Notably, the US Biomedical Advanced Research and Development Authority (BARDA) issued a broad agency announcement (BAA) in October 2015, which stated that: "BARDA will prioritize support for vaccines that induce broad immunity so as to prime the population against newly emerging influenza viruses or other respiratory viruses of pandemic potential." We see this as supportive to BiondVax's strategy to develop a primer, with the ultimate vision of the company is a truly universal flu vaccine.

Following completion of BVX-007 and BVX-008 (the last two ongoing Phase II trials) BiondVax is anticipating an end of Phase II meeting with the FDA in 2017-18 in preparation for the start of Phase III trials, potentially by end 2018. BiondVax signed an agreement with Cytovance Biologics in late 2015 for the upscaling, optimisation and contract manufacturing of M-001 in order to be ready for Phase III clinical trials in the 2017/18 timeframe. The company envisages a Phase III trial for one of the two primer indications. Further Phase III trials will expand to the remaining primer indication and subsequently the universal influenza vaccine indication.

Exhibit 2: BiondVax's development strategy and pathway to market



Source: BiondVax

Clinical testing to date: Encouraging immunogenicity data

So far, BiondVax has conducted two Phase I/II trials and three Phase II trials involving 479 young adults, older adults and elderly participants (the oldest being 91 years old) in total (Exhibit 3). All trials were randomised, placebo-controlled and single (Phase I/II) or double-blinded (Phase II). The studies enrolled healthy participants with the primary endpoints being safety/toxicity and immunogenicity as secondary endpoints. M-001 has been shown to be safe, well-tolerated and immunogenic, inducing both cellular and humoral immunity to multiple influenza strains.

Exhibit 3: Summary of completed trials with M-001

Trial	Age group	Year and Phase	Size (n)	Comments
BVX-002	18-49 years	2009, Phase I/II	63	The study demonstrated safety and immunogenicity of two doses of M-001 intramuscular injection with or without an adjuvant.
BVX-003	55-75 years	2010, Phase I/II	60	Safety and immunogenicity of two doses of M-001 intramuscular injection with or without an adjuvant was demonstrated in elderly.
BVX-004	18-49 years	2011, Phase II	200	In addition to more safety data (primary endpoint), the double-blind, placebo-control trial tested the idea of **seasonal vaccine priming** with M-001. The results demonstrated that increased humoral and cellular responses were detected after co-administration of adjuvanted M-001 with seasonal vaccine as compared to after co-administration of placebo with seasonal vaccine.
BVX-005	65 years+	2012, Phase II	120	In addition to more safety data (primary endpoint), the trial tested different **priming regimes** (one or two doses of 0.5mg of M-001; adjuvanted with aluminium phosphate or not) of vaccination with M-001 followed by seasonal vaccine in elderly population with the secondary endpoints being humoral (hemagglutination inhibition assay, HAI) and cell mediated (CD4+ and CD8+ lymphocytes producing IFN-gamma) immune responses. Results echoed previous trials showing safety and activation of both humoral and cellular responses. BiondVax revisited the study later on, when it exposed the blood plasma from the BVX-005 trial to H3N2 epidemic strain (2014/15) that did not exist in 2012. The immunogenicity was measured using HAI, which worked because M-001 was used as a primer to seasonal vaccine. The results showed that the level of protective antibodies against H31N2 was significantly higher in the M-001 primer group than in the control (seasonal vaccine only in 2012 study). Around of 50% of the participants in the M-001 group showed immunogenicity against the new strain versus only 10% in the control group (statistically significant).
BVX-006	50-64 years	2015, Phase II	36	Further safety and immunogenicity data from more intensive regimens: with regular 0.5mg (established in previous trials) and higher 1.0mg doses and three-dose regimen followed by seasonal vaccine. Results were consistent with the previous data and no significant side effects were noticed in the higher dose group. M-001 primed broader immune response than those strains included in the seasonal vaccine.

Source: BiondVax

BVX-005 study provides rationale for seasonal primer indication

Currently regulatory authorities evaluate seasonal vaccines based on HA antibodies, which correlate with protection. The M-001 vaccine does not induce the production of these antibodies, since it comprises only conserved epitopes. In order to demonstrate the efficacy of M-001 using the standard HA endpoint BiondVax conducted trials using M-001 as a primer to seasonal or pandemic vaccines. In trial BVX-005, where 120 elderly volunteers were randomised in four parallel groups and received either two doses of non-adjuvanted or adjuvanted M-001 or a single adjuvanted dose of M-001 or placebo.[4] All participants received conventional trivalent seasonal vaccine (TIV) afterwards. Results showed:

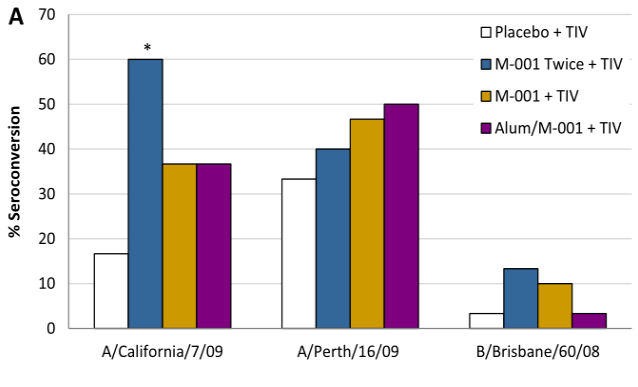
- **Humoral response to TIV strains**. Priming with M-001 had a positive effect on production of antibodies to the strains in the TIV vaccine (enhanced seroconversion and seroprotection; see Exhibit 4 and 5 for definitions); the difference between experimental arms and the control was not always significant due to small sample sizes. Seroconversion rates were more pronounced than seroprotection as the only criterion for the latter is titres of at least 1:40, which was already the case in some of the participants.
- **Humoral response to non-TIV strains**. Seroconversion to viruses not present in the seasonal vaccine was measured with an additional 11 viruses from H1N1 and H3N2 and influenza B strains (Exhibit 6); significant increases in antibodies to four viruses were obtained with greater response to all others when compared to priming with placebo. As expected, the response rates were not as high as to TIV strains. In our view, this demonstrates the cross-immunogenicity, which will be needed for a universal vaccine. For the standalone universal indication, in which only M-001 is used, and hence the current regulatory marker (HAI) cannot be used, the question of whether M-001 will be enough to elicit a broad protective effect against multiple influenza strains will need to be answered in Phase III trials.
- **Cell mediated immunity** was measured in the first 10 arriving participants from arms A (2 x M-001+ TIV) and C (1 x adj M-001 + TIV). Unlike the seasonal vaccine M-001 elicited response

[4] J. Atsmon et al. Priming by a novel universal influenza vaccine (Multimeric-001) – A gateway for improving immune response in the elderly population.Vaccine 32 (2014) 5816–5823.

from CD4+ and CD8+ cells that produced IFN-gamma (which plays an important role in clearing influenza virus infections, hence can be used as an indicator for M-001 efficacy).

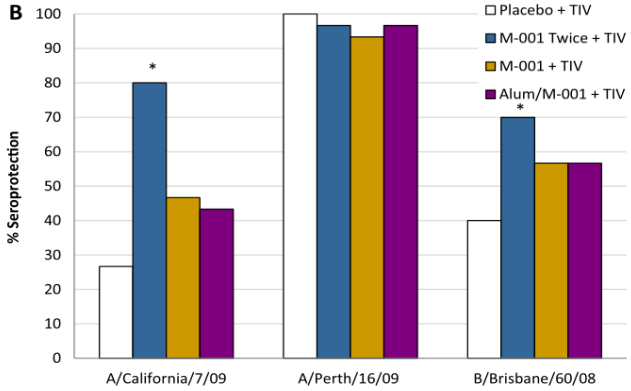
- **Adjuvanted M-001 formulation** was not superior to non-adjuvanted M-001; therefore, there is no benefit in the use of adjuvants, which renders M-001 more safe.

Exhibit 4: Seroconversion to TIV strains



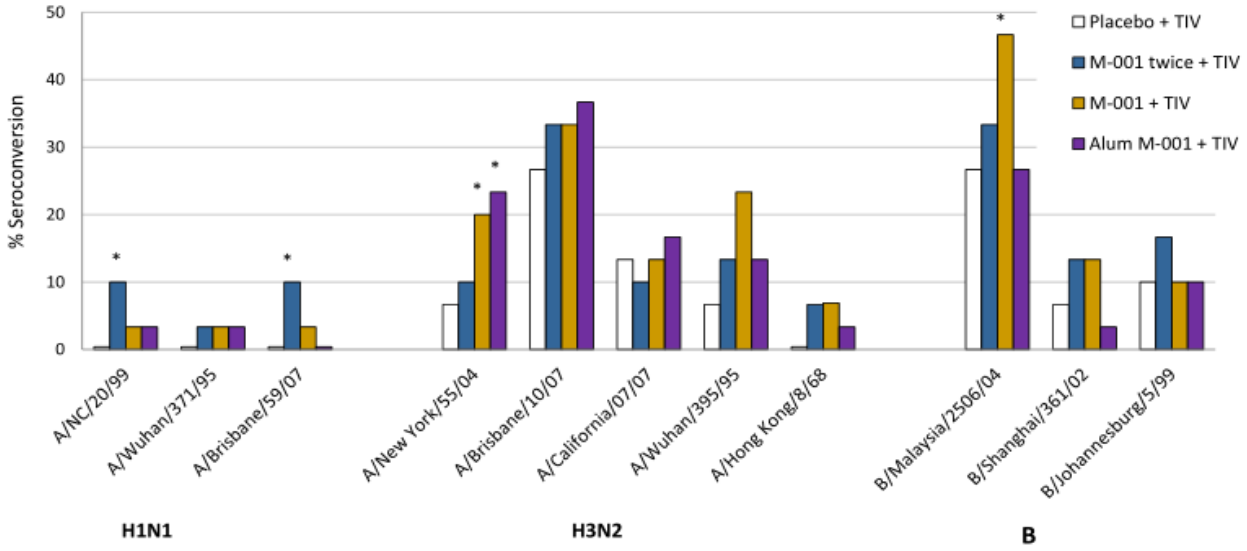
Source: Atsmon et al. Note: *p < 0.05 vs placebo. Seroconversion: the number of participants expressing a mean of ≥ fourfold increase in anti-HA antibody level compared to day 0 and reaching a titre level of ≥1:40.

Exhibit 5: Seroprotection to TIV strains



Source: Atsmon et al. Note: p < 0.05 vs placebo. Seroprotection: the number of participants per cohort expressing anti-HA antibody levels of ≥ 1:40 post-immunisation.

Exhibit 6: Seroconversion to non-TIV strains



Source: BiondVax, Atsmon et al. Note: *Significant difference between experimental and the control group p<0.05.

The last Phase II trials before moving to Phase III

BiondVax is conducting two further Phase II clinical trials in almost 400 adults in Europe and the US. In September 2015, trial BVX-007 was initiated in Hungary in collaboration with and financing from the UNISEC European Consortium. Apart from demonstrating safety and immunogenicity, the study aims to show (1) the use of M-001 for better pandemic preparedness, where it can be stockpiled and used immediately on any pandemic outbreak instead of waiting six months for the pandemic-specific vaccine to reach the market; and (2) the dose sparing potential of M-001 when given prior to suboptimal avian (H5N1) vaccine dose (Exhibit 7). This would be highly desirable in a pandemic when existing stockpiles of vaccine may be low. Enrolment is complete and results are expected end-2016/early-2017. In September 2015, BiondVax announced a collaboration with NIAID/NIH to commence trial BVX-008 in 180 adults in the US, which will be fully funded by the NIH. This trial will also assess M-001's ability to serve as a pandemic primer to H7N9 avian

pandemic vaccine. According to the latest update the trial could be initiated in coming months. The main question to be answered with Phase III trials with M-001 as a primer is the extent to which it will reproduce Phase I and II results. For a truly standalone universal vaccine it will be important to understand how long the protection lasts with the consensus being at least more than two to three years.

Exhibit 7: M-001: Final Phase II clinical trials

Trial	Aim	Design	Size (n)	Status	Results expected
Phase IIb BVX-007 (with UNISEC European Consortium)	M-001 as primer to pandemic influenza H5N1 (dose-sparing potential)	A randomised, double-blind, controlled trial. Primary endpoint safety and CMI response; secondary – HAI response to strain in the pandemic vaccine and non-pandemic strains, the association between CMI marker and humoral immune response. Three arms with doses of 0.5mg and 1.0mg of M-001 and placebo; suboptimal dose of adjuvanted 3mcg of H5N1 pandemic vaccine after M-001. Total monitoring for 180 days.	224 adults (18-60 years)	Last participant out in September 2016. Preliminary safety announced November 2016	End-2016/early-2017
Phase II BVX-008 (collaboration with NIH)	M-001 as primer to pandemic influenza A/H7N9	A randomized, double-blind, controlled trial. Primary endpoint safety; secondary – immunogenicity.	180 adults (18-60 years)	Start in H117	H217/H118

Source: BiondVax

BiondVax's multi epitope-based vaccine design vs conventional

Most current flu vaccines are subunit vaccines. The virus is grown, then inactivated and its surface antigens (eg HA) are used for immunisation. Other existing types of vaccines are live attenuated typically delivered as nasal sprays or injections.[5] These vaccines rely on triggering humoral (acquired) response to the variable surface regions of the influenza virus, therefore are highly strain specific.

There are two immune system types: innate and acquired. Innate is in-born, non-specific ability to defend against infections; acquired immunity is specific to a pathogen and is responsible for a long-lasting effect, eg vaccination. Most vaccines in use today work by inducing antibody-based immunity (acquired), but animal models and early-stage clinical trials have suggested that generating cellular immunity via T cell responses (innate) may induce broad protection that current vaccines lack. Furthermore, humoral immunity (antibodies) is effective against extra-cellular antigens, while a virus's life cycle is mainly inside the cells, and therefore not exposed to antibodies. Cell-mediated immunity is more effective against intra-cellular infections such as the influenza virus. The role of cellular immunity (innate) among others includes the direct clearance of virally infected cells, the indirect recruitment of other immune cells and also B cell stimulation (humoral response) leading to specific antigen antibody production.

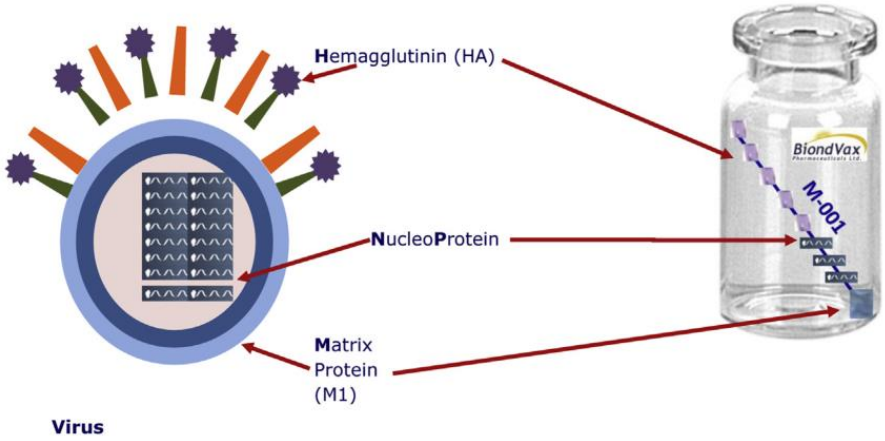
The conserved epitope-based approach focuses on the minimal component of a viral protein that activates the lymphocyte. Typically this corresponds to short peptides from 8-10 amino acids for the activation of T-cells and longer regions of up to 20 amino acids for activating B-cells.[4] Based on technology developed by Professor Ruth Arnon at the Weizmann Institute (Professor Arnon is also known as the co-developer of Copaxone, the blockbuster multiple sclerosis drug), BiondVax has designed a vaccine specifically to activate both the cellular (T-cells destroy virus infected cells) and the humoral (B-cells produce specific antibodies against the virus) arms of the immune system, both of which are now recognised to play an important role in controlling influenza infection.[2] A number of targets for influenza vaccine have been investigated by BiondVax and other researchers that would activate both T-cell and B-cell responses. These include conserved 'stalk' domain of hemagglutinin antigen, nucleoprotein (NP), Matrix 1 (M1) and Matrix protein 2 (M2e) among others.

The engineered 'multimeric' vaccine M-001 contains nine conserved and common epitopes (short peptides) from HA, M1 and NP viral antigens. The epitopes are combined into a single recombinant

[5] T. Gottlieb and T. Ben-Yedidia. Epitope-based approaches to a universal influenza vaccine. Journal of Autoimmunity 2014, 1-6.

protein easily manufactured in *E. coli* bacteria. These specific epitopes activate both arms of the immune system and were chosen to give broad (>90%) predicted HLA coverage in the human population.

Exhibit 8: In total nine conserved epitopes from HA, M1 and NP antigens comprise M-001



Source: BiondVax; T. Gottlieb and T. Ben-Yedidia. Epitope-based approaches to a universal influenza vaccine. Journal of Autoimmunity 2014, 1-6.

Prospects and challenges of a universal influenza vaccine

On 10 August 2016, BiondVax participated in the 'Eighth WHO meeting on development of influenza vaccines that induce broadly protective and long-lasting immune responses' held in Chicago, US. The WHO's Global Vaccine Plan calls for at least one licensed universal influenza vaccine by 2020 in response to poor effectiveness rates with conventional seasonal vaccines. The WHO monitors the progress and conducts periodic meetings with experts, who provide thought leadership about the development of innovative influenza vaccines. In our view, the clinical data so far and the positioning of M-001 are broadly in line with the consensus view about the universal vaccine. Still, several questions, such as Phase III trial design, regulatory pathway or protection effectiveness, will need to be answered. The main takeaways from the meeting regarding the prospects and challenges of the universal vaccine are described in Exhibit 9.

Exhibit 9: Key take aways from the WHO meeting	
Ideal candidate	The ideal universal vaccine candidate was described as one that "is safe, elicits humoral and cellular responses identical to those triggered by a natural infection, provides long-lasting and cross-strain protection, and can be manufactured rapidly in large amounts under well-controlled conditions." Next generation vaccine strategies will likely include more broadly reactive antibodies (anti-HA stem antibodies, antibodies against non-HA antigens, etc) and/or enhancement of cell mediated immunity (CMI).
Correlate of protection	Hemagglutinin inhibition assay is used to determine the immune response to seasonal influenza vaccines and can serve as a surrogate biomarker or relative correlate of protection for HA-based vaccines against laboratory-confirmed influenza virus infection because its correlation with protection is well established. This allows simplifying the clinical trials as demonstrating immunogenicity using biomarker can replace more onerous clinical endpoints. Therefore, lack of correlates for novel vaccines will require novel endpoints that will be determined in clinical efficacy studies in which the new candidate vaccine will have to demonstrate reduction of illness rate and severity. This will likely require larger clinical trials.
Assays	Methods to assess vaccines' effect will vary significantly depending of the mechanism of action. CMI assays are available and in use. Classic serologic (antibody) analyses may be appropriate for some vaccines, but new or modified assays for antibodies may be required.
Breadth and duration of immunity	This should last for at least two years against influenza A and both lineages of type B viruses. Safety is comparable to licensed vaccines.
Regulatory background	Regulatory pathways need to change for truly novel vaccines. Current guidance is applicable to HA-based seasonal or pandemic vaccines. Revised EU guidance at least considers non HA vaccines.
Potential design of late stage novel vaccine studies	Trial designs can vary significantly and will depend on specific indication. The range of designs can include comparative immunogenicity studies, although this is less likely for truly innovative vaccines due to different assays needed. Comparative efficacy trials against a licensed vaccine across several seasons, and non-inferiority or superiority endpoints in terms of efficacy can be considered. Continuous effectiveness or waning effectiveness with need to revaccinate will also need to be considered. Real world data post-vaccination epidemiologic monitoring is also a way to measure the long-term and broad efficacy of a new vaccine.
Potential product development pathways (GlaxoSmithKline perspective on second generation vaccines)	Vaccines may be initially targeted to specific sensitive groups like children, elderly or pregnant people or people with chronic conditions. Universal vaccines may be developed as protective/priming pandemic vaccines and could be used for stockpiling. Influenza B strain cannot be ignored as it is also a highly morbid infection and second only to H3N2 in terms of causing hospitalisation and death among all ages. Seasonal quadrivalent vaccines protecting against both B lineages will likely be standard of care by 2020. The efficacy of a universal influenza vaccine should be non-inferior to standard of care for at least two to three years and without annual boosting. Optimal late stage trial design could include three arms with placebo and licensed vaccine controls and will likely last four to five years. The transition from seasonal trivalent vaccines to quadrivalent provide a good example, so the transition to an effective universal vaccine will be gradual and will depend on product claims and supporting data, the licensing situation, use recommendations and cost efficiency. Notably, other parties in attendance at the WHO meeting had different perspectives from GSK's, raising issues regarding the complexity of comparisons of effectiveness. There was no final agreement.

Source: Edison Investment Research, World Health Organization (WHO)

Competitive landscape and differentiation

M-001 is clearly differentiated from conventional seasonal vaccines (Exhibit 10). More importantly, the initial positioning is to provide a priming boost in order to increase the effectiveness of seasonal or pandemic vaccines. If the Phase III study confirms the synergy of priming seasonal or pandemic vaccine in a form of either increased efficacy or broadened coverage (ie reduced virus-vaccine mismatch), or decreased dose of a seasonal/pandemic vaccine, this, in our view, could present a strong case for M-001. We also expect that, subject to regulatory approval, the early adopters of M-001 as a primer for seasonal vaccine could come from the private sector, with public recommendations and more clarity on reimbursement level following. BiondVax is also among the leaders in the race to develop a universal influenza vaccine (Exhibit 11).

Exhibit 10: Key advantages of the BiondVax universal flu vaccine	
BiondVax M-001	**Conventional flu vaccine**
Broader immune system activation: designed to activate antibodies (humoral response) and specific T and B lymphocytes (cellular response); potentially more effective in elderly; evidence of cross-protection to other strains; can enhance the action of conventional vaccines.	Often limited to anti-HA antibody induction. No cross immunity conferred to non-vaccine strains.
Broad coverage of strains: covers different type A and B seasonal and pandemic influenza strains, both current and future.	Limited to 2 A strains and 1-2 B strains. Requires new vaccine each season and separate stockpiles for each pandemic with a limited possibility that the correct strain was stockpiled.
Shorter production time: 6-8 weeks. Invaluable in a pandemic outbreak	Long production time: 16-24 weeks lead-time. Requires forward planning
Year round production, ability to stockpile: M-001's conserved peptide components eliminate the need to reformulate the vaccine every season; enables year-round, flexible production and stockpiling according to demand.	Inflexible: the WHO selects three to four strains in Q1 each year; these are produced and distributed in the Northern Hemisphere during September to November.
Egg-free production method in bacterial system.	Egg-based manufacture: lengthy, costly and can cause allergic reactions.

Source: Edison Investment Research, BiondVax

Exhibit 11: Universal flu vaccines in clinical development

Company (product)	Technology	Status	Differentiation
BiondVax (M-001)	Synthetic B and T cell conserved epitopes (9)	Multiple Phase II reported (n = 479), Phase IIb ongoing	Broad strain coverage, clinical data in adults/elderly. Stimulates CTL and antibody response.
Imutex, SEEK/hVIVO JV (Flu v)	T cell peptides (6), conserved epitopes	In Phase IIb in Europe and Phase II in US (joint with NIH) started in August 2016	Potentially cross-protective; stimulates CTL and antibody response.
Altimmune (NasoVAX)	Recombinant vaccine in replication deficient adenovirus	Phase I complete (n= 217); ready for Phase II	Intranasal. Stimulates CTL and antibody response.
Inovio (SynCon platform)	Synthetic DNA "constructs" for selected type A and B seasonal and pandemic subtypes	Phase Ib appears complete (2012) – seeking funding	Vaccine capable of generating strong T cell response.
FluGen (Redee Flu)	Single replication virus M2SR with inserted HA/NA antigens	Preclinical, funds raised for Phase I to start 2016	Animal data shows cross-protection potential. Stimulates CTL and antibody response.
Okairos (viral vector platform) acquired by GSK for $325m	T cell vaccine, adenovirus vector	Preclinical	Animal data shows cross-protection potential.

Source: Edison Investment Research

Sensitivities

BiondVax is subject to the usual risks associated with R&D, including clinical development failures, regulatory risks, competition, partnering setbacks and financing and commercial risks. The biggest near-term sensitivities are related to the outcomes of the currently running Phase IIb trial (BVX-007) with M-001 in Europe and the second Phase II trial (BVX-008) to be initiated in the US. Subsequent to this, obtaining a strong partner willing to invest in costly Phase III studies will be crucial for timely development progression. However, alternative non-dilutive funding opportunities may also exist such as regional royalty-based licensing or distribution agreements. This, however, might not be an issue depending on the data gathered in the ongoing clinical trials and given the fact that the need for a universal flu vaccine is supported by the consensus (eg the WHO) and represents an attractive market. Although, as discussed, M-001 will be a clearly differentiated influenza vaccine, the eventual market uptake is difficult to forecast. We also note that, as revealed in March 2016, CEO Ron Babecoff is currently under investigation by the Israel Securities Authority for potential relations to persons involved in an insider trading case in BiondVax shares, although the company is not a party to the investigation. The CEO continues to perform his role with no restrictions or limitations.

Valuation

We value BiondVax based on a risk-adjusted NPV analysis using a 12.5% discount rate and including NIS28.6m ($7.5m) net cash estimated at end of 2016. This corresponds to a value of NIS269m ($71m) or NIS2.0/sh ($21.0/ADR). If we include c 116m outstanding options and warrants, the relative valuation on a fully-diluted basis would be NIS1.1/share ($11.3/ADR). Exhibit 122 provides assumptions and our valuation of M-011 in each indication separately. We have included two of the three indications envisioned by BiondVax, namely primer for pandemic vaccines and primer for seasonal vaccination for populations at risk. The company has indicated that the priming direction is likely the fastest way to the market and that both indications (pandemic or seasonal vaccine primer) have the same priority, with the final development plan to be discussed with the future partner. For the purpose of our valuation, we assume that pandemic primer will be the first indication with seasonal primer following. M-001 as standalone universal influenza vaccine is clearly the ultimate goal, however the most R&D intensive route as well. This would be a paradigm shift and would reshape the flu vaccine industry, thus the visibility of such changes is low currently, and hence we do not include this in our valuation yet, but provides a potential upside.

Exhibit 12: Sum-of-the parts summary of BiondVax valuation

Product	Launch	Peak sales ($m)	Full rNPV ($m)	Technology probability	Licensing deal probability	BiondVax's rNPV ($m)	rNPV/ADR ($)	rNPV/share (NIS)	Comments
M-001 as pandemic vaccine primer	2023	670	159.2	60%	30%	37.7	11.15	1.06	Full rNPV reflects the valuation as if BiondVax develops and markets M-001 standalone assuming all associated costs. The licensing deal was modelled on a basis of full rNPV split at 25% (BiondVax):75% (partner).
M-001 as seasonal vaccine primer	2027	1,380	122.9	60%	30%	25.7	7.62	0.72	
								0.00	
Net cash ($)			7.5	100%		7.5	2.23	0.21	
Valuation ($)			**289.7**			**70.9**	**21.00**		
Valuation (NIS)			**1,098.4**			**269.0**		**1.99**	

Source: Edison Investment Research. Note: WACC = 12.5% for product valuations.

Assumptions

We use a risk-adjusted NPV method to value each indication separately (one project per indication), hence have made a number of assumptions for each of the projects. For the projects we have used industry standard assumptions where available. Probabilities to reach the market and timelines were selected according to the stage of the project, noting however, probabilities published in the literature mostly relate to drugs. We include a 60% chance that M-001 will be successful given the advanced Phase II stage. While M-001 has substantial clinical data supporting its immunogenicity, the Phase III trials will ultimately demonstrate whether this will translate to clinical efficacy, which would be the basis for the approval. We also include licensing deal probability of 30%, which is rather conservative, but in our view to some extent reflected in the company's current market valuation of just NIS46m ($13m) or EV of NIS25m ($6.6m). Therefore, a licensing deal would warrant a significant revaluation according to our model. Product launch dates were estimated based on the additional trials needed. BiondVax's strategy is to seek a partner ahead of the Phase III studies; we therefore include a licensing deal in our model for both indications. BiondVax may also receive grants and/or matching funds from US and European government sources, since improved flu vaccines are a stated priority.

Pandemic primer indication

For the calculation of target patient groups, we use the US population plus top five European countries and Benelux, the Nordics and Austria with Switzerland. For the pandemic vaccine primer indication, we assume that in the case of proven efficacy, governments would buy M-001 for national stockpiles meant to protect critical workforces in case of an outbreak. In the US we assume that it would constitute around 15% of the population (15% equals c 49 million people; eg BARDA has a goal to stockpile for 20 million of critical workforce with vaccines for one clade of H5N1) and a more conservative 8% in Europe due to the fragmented market. We also assume that it would take two to three years to reach a supply agreement and build up the stockpile. Subsequently, one-third of the stockpiled vaccines would need to be replaced annually, which mostly drives the value for this indication and translates into c 16m vaccine regimes shipped per year in the US and c 8.5m in Europe. The current trivalent vaccine price per dose in the US is around $8-9 and quadrivalent $13-15,[6] indicating that quadrivalent vaccines managed to attract a premium, although whether the additional protection against type B virus confers a clinical benefit is still not clear. We assume a price of $25 per regimen (likely two shots).

Seasonal primer indication

According to EvaluatePharma, the worldwide influenza vaccine market was $4.3bn, with Fluzone (Sanofi, quadrivalent) reaching top $1.5bn in sales in 2015. For the seasonal primer indication

[6] www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/ accessed 22 11 2016

BiondVax has defined the primary target population as mainly the elderly population, which will likely represent the first market for M-001. In our view, there is clearly a potential beyond the population at risk, therefore in our model we aimed to capture broader groups that may be interested in using a universal flu vaccine. For example, after the regulatory approval, there might be an initial pull from the private sector until the vaccine gets wide reimbursement coverage. Currently around 45% of people in the US are vaccinated against influenza with this number being relatively stable over the past five to six seasons (CDC) and indicating a realistic market for M-001. We assume that M-001 would penetrate 25% of this population over a seven-year period. This conservative assumption reflects the novelty of the technology and the associated uncertainty of the commercial strategy. Currently CDC recommends that everyone six months of age or older should get a flu vaccine, which shows a very proactive stance aiming for full protection, as opposed to European countries, where recommendations vary significantly, with the only unanimous recommendation for age groups being to elderly people. In our view, M-001 market uptake would be substantially affected by what recommendation level M-001 reaches.

We assume slightly more conservative inputs when modelling M-001 in European countries. Currently only up to around 25% of the population is vaccinated in Western European countries, which we use as a target population and assume same 25% penetration rate.

Costs and licensing deal assumptions

BiondVax has indicated that partnering for Phase III is one of the strategic directions alongside seeking all available non-dilutive financing, as Phase III innovative flu vaccine trials tend be costly, long and include thousands of patients.[7] We assume a Phase III start for the pandemic primer indication in 2018 and regulatory approval in 2022, while the seasonal primer indication could start in 2023 and reach the market in 2027. We assume total costs of $50m per trial. Commercial assumptions include 10% COGS, and 15% sales and marketing expenses in the pandemic primer indication and 25% in seasonal vaccine. Also we assume a 3% pay away from net sales to original licence holder Yeda Research. Notably, 20% of consideration received up to the first $20m in milestones and 15% of consideration thereafter will also be paid away to Yeda, however it could potentially wait until M-001 reaches the market before asking for its share of milestones.

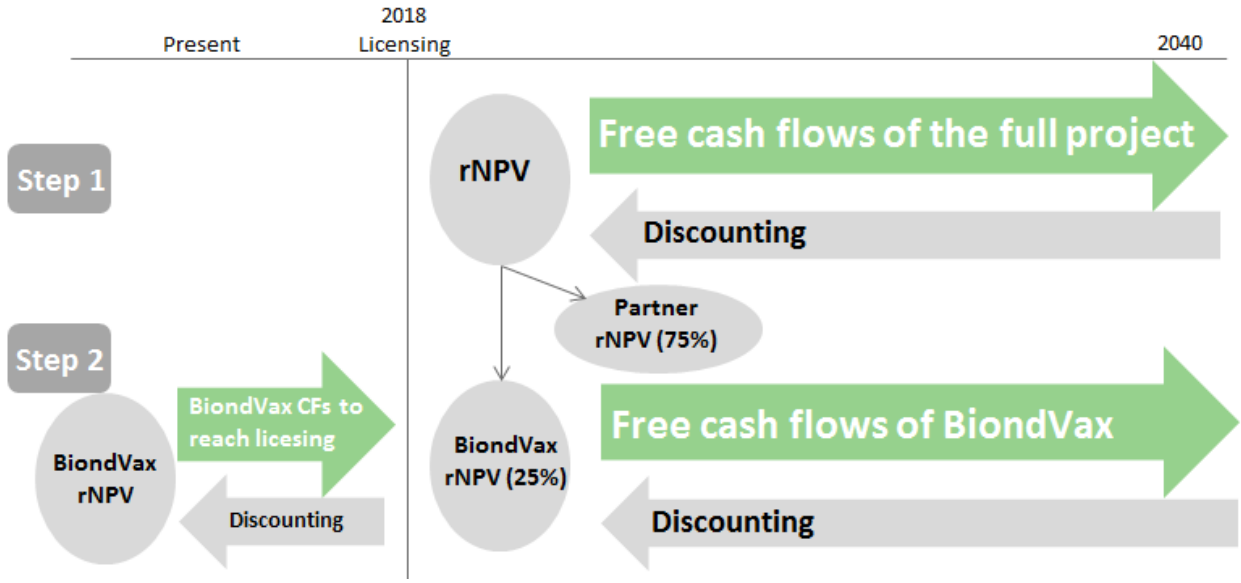
Licensing deal assumptions and calculations

When it comes to influenza and innovative vaccines, there is a lack of licensing deals that could be considered comparable. We therefore model the licensing deal bottom-up starting with the full rNPV project including all development and commercialisation costs (Exhibit 13). We assume that BiondVax will out-license M-001 in mid-2018, but currently there is no visibility of the level of the Phase III costs that BiondVax could co-finance. We therefore assume that M-001 will be wholly out-licensed and BiondVax will not incur any additional costs. We assume that BiondVax and the partner would negotiate a value split with BiondVax retaining 25% of the full project rNPV at the time of licensing. If BiondVax co-financed the development, this would significantly increase the value split and the deal terms (discussed below) for BiondVax. After separating cash flow lines and discounting, we calculate rNPVs for both licensor (BiondVax) and licensee (the partner) at the time of the licensing, assumed in 2018. In order to justify the 25%:75% split, we calculate that the deal terms for the pandemic primer indication could be tiered royalties starting at 10% and rising to 13% depending on net sales. Total upfront and milestones (development and commercialisation) could be around $133m. As mentioned, the deal terms are subject to increase if BiondVax is able to co-finance the Phase III trial and we will revisit our calculation once more details emerge. Similarly, for the seasonal primer indication, we calculate 10%+ royalties and total upfront and milestones of $174m. We arrive at a final rNPV for BiondVax by discounting the company's share of the full rNPV

[7] A. Chit et al. Toward more specific and transparent research and development costs: The case of seasonal influenza vaccines. Vaccine (2013).

and adding costs needed to reach the assumed licensing in 2018; guided burn is $250k/month, so we include $5m covering Q416-H118.

Exhibit 13: Schematic representation of BiondVax cash flows



Source: Edison Investment Research

Financials

BiondVax is debt-free and we estimate cash and cash equivalents (cash, cash equivalents and short- and long-term marketable securities) of NIS28.6m ($7.5m) at the end of 2016 compared to NIS37.5m ($9.9m) by end-2015. R&D expenditures totalled to NIS1.5m ($385k) in Q216 and were lower year-on-year (NIS2.6m [$686k] in Q215). Notably, BiondVax is able to run its operations in such a lean way since its partners UNISEC in Europe and NIH in the US are funding the majority of the costs associated with the Phase II studies. BiondVax indicated that the cash burn is around $250k per month, which implies cash reach to 2019 assuming a similar level of activities. Therefore transition to Phase III studies is reachable with current cash, but this will likely be with a partner on board, although the company has indicated that it will explore all options for Phase III funding. So far, BiondVax has received c $3.6m in OCS grants (Office of the Chief Scientist [Israel] grants), which are off balance sheet royalty-based liabilities.

Exhibit 14: Financial summary

NIS'000s	2013	2014	2015	2016e	2017e
December	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	0	0	0	0	0
Cost of Sales	0	0	0	0	0
Gross Profit	0	0	0	0	0
Research and development	(5,451)	(5,492)	(7,906)	(7,906)	(7,906)
EBITDA	(6,932)	(7,465)	(10,675)	(10,673)	(10,673)
Operating Profit (before amort. and except.)	(7,627)	(8,142)	(11,303)	(11,303)	(11,303)
Intangible Amortisation	(14)	0	0	0	0
Exceptionals	0	0	0	0	0
Other	0	0	0	0	0
Operating Profit	(7,641)	(8,142)	(11,303)	(11,303)	(11,303)
Net Interest	(395)	378	1,104	580	496
Profit Before Tax (norm)	(8,022)	(7,764)	(10,199)	(10,723)	(10,807)
Profit Before Tax (reported)	(8,036)	(7,764)	(10,199)	(10,723)	(10,807)
Tax	0	0	0	0	0
Profit After Tax (norm)	(8,022)	(7,764)	(10,199)	(10,723)	(10,807)
Profit After Tax (reported)	(8,036)	(7,764)	(10,199)	(10,723)	(10,807)
Average Number of Shares Outstanding (m)	47.9	54.3	105.5	135.1	135.1
EPS - normalised (NIS)	(0.17)	(0.14)	(0.10)	(0.08)	(0.08)
EPS - normalised and fully diluted (NIS)	(0.17)	(0.14)	(0.10)	(0.08)	(0.08)
EPS - (reported) (NIS)	(0.17)	(0.14)	(0.10)	(0.08)	(0.08)
Dividend per share (NIS)	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	N/A	N/A	N/A	N/A	N/A
EBITDA Margin (%)	N/A	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET					
Fixed Assets	5,458	5,753	4,379	3,749	3,120
Intangible Assets	0	0	0	0	0
Tangible Assets	3,285	2,638	2,044	1,414	785
Investments	2,173	3,115	2,335	2,335	2,335
Current Assets	20,365	12,709	36,928	27,834	18,402
Stocks	0	0	0	0	0
Debtors	489	1,081	1,442	1,262	1,262
Cash	17,863	9,612	33,470	24,557	15,124
Other	2,013	2,016	2,016	2,016	2,016
Current Liabilities	(1,782)	(1,813)	(1,699)	(1,953)	(1,953)
Creditors	(1,782)	(1,813)	(1,699)	(1,953)	(1,953)
Short term borrowings	0	0	0	0	0
Long Term Liabilities	(55)	(62)	(69)	(69)	(69)
Long term borrowings	0	0	0	0	0
Other long term liabilities	(55)	(62)	(69)	(69)	(69)
Net Assets	23,986	16,587	39,539	29,561	19,499
CASH FLOW					
Operating Cash Flow	(4,338)	(7,624)	(10,262)	(9,494)	(9,928)
Net Interest	133	52	(5)	580	496
Tax	0	0	0	0	0
Capex	(196)	(30)	(34)	0	0
Acquisitions/disposals	0	0	0	0	0
Financing	9,248	(782)	33,753	0	0
Other	1,987	133	406	0	0
Dividends	0	0	0	0	0
Net Cash Flow	6,834	(8,251)	23,858	(8,913)	(9,432)
Opening net debt/(cash)	(11,029)	(17,863)	(9,612)	(33,470)	(24,557)
HP finance leases initiated	0	0	0	0	0
Other	0	0	0	(0)	0
Closing net debt/(cash)	(17,863)	(9,612)	(33,470)	(24,557)	(15,124)

Source: Edison Investment Research, BiondVax accounts. Note: Liquid cash resources = cash, cash equivalents and short- and long-term marketable investments.

Contact details	Revenue by geography
14 Einstein Street Ness Ziona – 7403618 Israel +972 8 930 2529 info@biondvax.com	N/A

Management team

Co-Founder, President and CEO: Dr Ron Babecoff	Chief Scientific Officer: Dr Tamar Ben-Yedidia, PhD
Dr Ron Babecoff co-founded BiondVax in 2003 and has served as CEO since then. Prior to this, he worked for 10 years in marketing and development in the pharmaceutical industry, including as a marketing manager in at Omrix Biopharmaceuticals. Dr Babecoff holds a DVM degree from the University of Liège, Belgium and a master of entrepreneurship and innovation from the Swinburne University of Technology of Melbourne, Australia.	Dr Tamar Ben-Yedidia joined BiondVax in 2004 as director of R&D after 15 years of experience in immunology and vaccine development. In 1994 she joined the Weizmann Institute of Science, where she worked on the design of a peptide-based vaccine against several pathogens and focused on influenza. Dr Ben-Yedidia received her PhD from the Weizmann Institute for her work on the peptide-based vaccine against influenza.
Chief Operating Officer: Dr Shimon Hassin, PhD	**Chief Financial Officer: Uri Ben-Or, CPA, MBA**
Prior to joining BiondVax, Dr Hassin worked in the biotechnology industry for 10 years in various positions including co-founder and CEO of Kadimastem, a developer of artificial pancreas, and head of process development at InSight Biopharmaceuticals, a biosimilar drugs developer. Dr Hassin holds a PhD in biotechnology from the University of Maryland Biotechnology Institute.	Mr Ben-Or provides his services through CFO Direct, a company which he founded and where he is the CEO. Prior to this he served as VP, Finance of Glycominds, a biotechnology company, and as CFO of a spin-off from Telrad Networks. Mr Ben-Or holds a BA degree in business from the College of Administration and an MBA degree from the Bar Ilan University.

Principal shareholders	(%)
I.B.I Mutual Fund Management	6.70
Ron Babecoff	4.09
George H Lowell	0.26
Avner Rotman	0.12
Tamar Ben-Yedidia	0.11
Uri Ben-Or	0.11
Vantage Investment Advisory Limited	0.01

Companies named in this report

Sanofi (SAN), GlaxoSmithKline (GSK), Imutex, Altimmune, Inovio, FluGen, Okairos

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