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Bavarian Nordic (BAVA DC/BVNRY)

No Upside from Flawed and Unproven Infectious-Disease "Platform"

On September 15, Bavarian Nordic announced that it had received a $9mm subcontract from Crucell (a subsidiary of Johnson & Johnson) to support Crucell's own contract with the US Department of Health and Human Service to further the development of its Ebola prime-boost vaccine regimen (with Bavarian Nordic's MVA-BN-Filo serving as the boost). Even though $9mm (spread out over four years) means very little in the context of a [[$1.2B]] company, this development has apparently sparked renewed interest in Bavarian Nordic's infectious-disease business.

However, when assessing the value of this business, investors need to bear in mind a few key points:

1) The Ebola outbreak in Africa has almost ended, with very few new cases emerging in a small number of countries, and experts continue to believe that new cases will drop to zero by the end of the year.

2) Two other vaccine candidates – one from Merck (rVSV-ZEBOV-GP) and one from GSK (ChAd3-EBO-Z) – are far more developed than the Crucell/Bavarian Nordic regimen. rVSV in particular already has Phase 3 data indicating real-world vaccine efficacy of 100% in a 7,651-person trial. As a result, on-the-ground interest in *other* vaccine candidates has fallen off drastically. Moreover, since it requires only one dose, rVSV is substantially more practical than the Crucell regimen, which requires patients to receive follow-up injections, potentially in the midst of a chaotic outbreak. While we expect research into other candidates to continue, rVSV is indisputably the front-runner, and the Crucell regimen is, at best, a distant third.

3) No commercially available vaccines work the way that Bavarian Nordic hopes its MVA "platform" will work – including the company's single successful product, Imvamune, which is simply a less virulent version of vaccinia, which in turn is a cousin of the smallpox virus itself. Proven vaccines use inactivated or killed pathogens, attenuated pathogens (like Imvamune), or purified pathogen components (like the viral proteins used in HPV vaccines). By contrast, Bavarian Nordic believes it can simply insert genes derived from other viruses into MVA – which, since it can't replicate in humans, is naturally less immunogenic than typical vaccines – and achieve an adequate immune response to the insert and not just to the MVA.

> But there is little reason to expect this to work well or consistently. Indeed, as a standalone agent, MVA-BN-Filo – the Ebola boost – appears to be only very weakly immunogenic in humans, explaining why it's only being assessed as part of a combination and not as a vaccine in its own right. In other areas, like HIV, vaccine candidates using other viruses as vectors have not only failed but even, in some cases, *harmed* patients, e.g. *increasing* the probability that they would contract HIV. If creating effective vaccines were truly as simple as just inserting pathogen genes into an unrelated vector, then scientists would have eradicated malaria, HIV, hepatitis C, and other infectious diseases decades ago. There is no evidence that Bavarian Nordic has an innovative or advanced approach that would allow it to succeed where others have failed; rather, as with Prostvac, it simply chooses to believe that those failures have no bearing on its own efforts.

In short, beyond smallpox, Bavarian Nordic's infectious-disease "platform" is unproven, embodies no special insights, any has already failed to produce a winner in the Ebola space; it is extracting money from the US government only by tagging along with another company's project.

The Ebola Outbreak Is Almost Over, and rVSV Is the Leading Vaccine Candidate

The latest data from the World Health Organization show that, for the past several months, new cases of Ebola have slowed to just a handful per week; Guinea just achieved its first Ebola-free week in over a year. While the outbreak has been stubbornly difficult to *fully* resolve, researchers continue to believe, in the words of one, that "it'll be not too long before we go down to zero." Bruce Aylward, Special Representative on Ebola Response for the World Health Organization, echoed this sentiment just last week, saying, "Our goal is zero transmission in the human population and that remains very possible within 2015." Tellingly, the US government announcement of the Crucell contract focused on "be[ing] fully prepared for the future" rather than on addressing the current outbreak. Old visions of Bavarian Nordic's supposedly huge Ebola opportunity – one sell-side analyst wrote last October about "mass vaccination" and "conservatively model[ed] in an additional 1m dose contract over 2015/2016" – now appear wildly unrealistic.

What has also changed is the advent of strong clinical data for a vaccine candidate that, unfortunately for Bavarian Nordic, the company has nothing to do with. rVSV-ZEBOV-GP, originally developed by the Canadian government and now backed by Merck, achieved 100% efficacy in a published Phase 3 trial that compared population clusters vaccinated immediately with those vaccinated only after a multi-week delay. At an individual patient level, after allowing for a 10-day incubation period for latent infections, no one who received the vaccine in either group went on to develop Ebola. While questions remain about whether this 100% efficacy will be replicated in future studies, the international medical community has clearly embraced rVSV as a success, with the philanthropic group Wellcome Trust, for instance, calling it a "breakthrough" and "incredible." Indeed, in the words of one media report, the "independent committee overseeing the trial considered the preliminary results so convincing that the control group was dropped on 26 July, and all contacts [of individuals infected with Ebola] are now

being vaccinated immediately." According to *Science*, all the enthusiasm for rVSV has already impaired efforts to study the GSK vaccine (let alone Bavarian Nordic's even earlier-stage product):

> The plan was to set up a separate ring vaccination study for the GSK vaccine, but that seems impossible now, Kieny [an assistant director-general at WHO] says; the Guinean government wants to stick with the proven vaccine, until Ebola is gone.

Even rVSV, however, is unlikely to be stockpiled in great quantities, according to the Washington *Times*:

> It's unlikely an Ebola vaccine will join chickenpox, measles and tetanus shots as standard for the general population, but officials will have to decide how much of the vaccine to stockpile, and whether to require mandatory vaccination for those with high-risk jobs.
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> "The one thing that's clear to me is that we will be vaccinating lab workers who work with Ebola," said Dr. Cliff Lane of the National Institutes of Health, co-principal investigator on the vaccine trial in Liberia.
>
> Amesh Adalja, a senior associate at the University of Pittsburgh Center for Health Security, said the U.S. might vaccinate certain members of the military and health workers in Ebola "hot spot countries," but not Americans at large.
>
> "Understanding how much will be needed will be difficult as traditional Ebola outbreaks have been much smaller historically than the West African outbreak," he said. "Likely modeling studies and prior outbreak sizes will inform the effort."
>
> … The compound rVSV-ZEBOV was singled out because it's one of the two most advanced vaccines under development today and showed promise in primate testing. The other, developed by GlaxoSmithKine, uses a chimpanzee cold virus and is part of the Liberia study.

Notably, the article doesn't even mention the Ad26/MVA vaccine in which Bavarian Nordic has played a part. But even if that vaccine worked as well as rVSV, it would have a major logistical drawback: the requirement of a boost. rVSV is effective as a single shot. Researchers noted this practical advantage even before the current outbreak:

> [A]lthough laboratory and healthcare workers and some military personnel in stable settings with defined risk may be candidates for a multidose vaccine, outbreak settings require protection that is rapidly conferred with a single administration.

While one sell-side analyst recently argued that Bavarian Nordic "could be ideally positioned to capture Ebola vaccine supply contracts, just as it did for smallpox," the analogy makes little

sense. There is no evidence that the Ad26/MVA vaccine is even clinically effective in humans, and, given the dearth of new cases, such evidence may never exist. Even for rVSV, any "supply contracts" are likely to be modest in size given the focus on a small number of front-line workers in affected countries. Moreover, while Ebola is certainly a dangerous pathogen, the current outbreak – the largest ever – has killed approximately 11,000 people. Smallpox, by contrast, killed *hundreds of millions* throughout the 20th century. Ebola transmission requires direct contact with infected bodily fluids, while smallpox can be airborne and spreads via respiratory droplets. Clearly smallpox is much more daunting as a potential bioweapon. In the case of smallpox, Bavarian Nordic's MVA strain was a close relative to the traditional vaccine vector and thus a logical candidate; by contrast, MVA has little to do with Ebola, and, as we discuss below, MVA-BN-Filo on its own triggers very few immune responses. Any optimism about Bavarian Nordic's future profits from Ebola is misplaced.

Bavarian Nordic's Infectious-Disease "Platform" Is Flawed and Unproven

Some observers argue that Bavarian Nordic should be viewed as a vaccine "platform" company, able to address not only smallpox and perhaps Ebola but other targets as well. However, vaccine development is no simple matter; if it was, the CDC's "List of Vaccines Used in the United States" would cover more than just 24 diseases. These successful vaccines generally employ inactivated or attenuated forms of the underlying pathogens; they don't use unrelated viral vectors (as is Bavarian Nordic's strategy). In Ebola, rVSV does use vesicular stomatitis virus as a vector, but it swaps out the native VSV protein coat for the Ebola virus's; thus, to the immune system, the vaccine "looks" like Ebola, not just an unrelated virus that happens to manufacture some Ebola proteins on the side. That approach might work in some instances but would tend to run into the same problem of immunodominance that we have highlighted in the context of Prostvac: the immune system is likely to attack the underlying vector (MVA), which offers many of its own antigens to target, rather than home in on the gene products of the pathogen that the vaccine is actually supposed to ward off.

Indeed, for Ebola, this isn't just a theory. Based on early data disclosed to the FDA, we know that, on a standalone basis, MVA-BN-Filo elicits few Ebola-specific immune responses, both on an absolute basis and relative to the Ad26 prime:

	% of patients categorized as "responders" by Day 29	
Immunity type	*MVA-BN-Filo*	*Ad26.ZEBOV*
Humoral (ELISA)	20%	97%
Cellular (CD4+ T cell)*	10%	37%
Cellular (CD8+ T cell)*	0%	57%

**Using HIV Vaccine Trial Network (HVTN) definition of "responder."*
Source: "Janssen Ebola Vaccine Program Update FDA Advisory Committee" (May 2015), Kerrisdale analysis

While almost all Ad26.ZEBOV recipients mounted a significant humoral (antibody) immune response to Ebola, just 20% of MVA-BN-Filo recipients did. More than half of Ad26.ZEBOV recipients saw CD8+ T-cell responses, while, under the same definition of "response," *none* of MVA-BN-Filo recipients did. Researchers do believe that adding an MVA boost to the Ad26 prime can strengthen it, but the failure of the MVA vaccine in humans to reach immunogenicity, let alone efficacy (a far higher bar), offers hard evidence of the weakness of the Bavarian Nordic "platform." If it were truly a "platform," then in principle the company could add any viral protein to MVA and thereby produce an effective vaccine for that virus. Indeed, one old annual report highlighted the company's "vaccines [*sic*] programmes against HIV, smallpox, Japanese encephalitis and Dengue Fever." But the results in Ebola demonstrate that this "plug and play" approach drastically underestimates the difficulties; HIV, for instance, has not been conquered, by Bavarian Nordic or anyone else.

HIV does offer an interesting cautionary tale, however, as a very recent journal article explains (emphasis added):

> Developing a safe and effective vaccine against HIV-1 acquisition remains a public health priority and a scientific challenge three decades after the discovery of the HIV-1 virus and the launch of the first HIV-1 vaccine clinical trial. Of the six large-scale HIV-1 vaccine efficacy trials conducted in humans to date, only [one]…has shown a modest prevention effect (31%). Two earlier trials…and a recent trial…showed no efficacy. Two other trials of a rAd5-vectored vaccine expressing HIV-1 internal proteins Gag, Pol and Nef also showed no vaccine efficacy **and raised the possibility of increased HIV-1 acquisition in the vaccine group** despite clinical safety and immunogenicity demonstrated in multiple phase 1/2 studies.

Using more mature follow-up data, the article confirmed that the rAd5 vaccine *did* substantially increase the risk of HIV acquisition relative to placebo, noting that "[a] biological mechanism to explain the increased risk…has not been identified." In short, multiple serious efforts to devise an HIV vaccine by inserting HIV genes into relatively harmless viruses have failed to achieve any meaningful results. The same thing is true for malaria: many viral-vectored malaria vaccine candidates have been studied, yet the only thing close to a malaria vaccine that currently exists (and is only modestly effective) consists of recombinant protein and does not use such a vector.

In sum, Bavarian Nordic's infectious-disease "platform" is based on an unproven approach to vaccine creation that has historically achieved very little and, in Bavarian Nordic's case, has already demonstrated almost no efficacy against Ebola. There is no good reason to expect it to ever generate substantial value.

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