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deltaFLU:
Clinical-Stage Influenza Vaccine for Broad Cross-Protection and Greater Efficacy

Vivaldi Biosciences is developing its deltaFLU genetically attenuated influenza vaccine to provide broad cross-protection and superior efficacy in the prophylaxis of seasonal and pandemic influenza. Vaccination is the primary means of preventing influenza infections and their spread, but effectiveness of conventional influenza vaccines ("flu shots") typically is only 40-60%, and is far lower in some years.

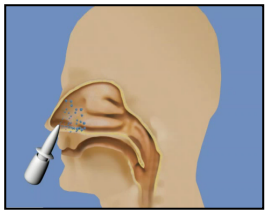
Conventional flu shots aim to provide protection against influenza by stimulating serum antibodies to the neuraminidase (NA) and / or hemagglutinin (HA) antigens of the influenza strains of which they're composed. Influenza viruses have a high rate of genetic mutation, causing changes in the HA and NA antigens that impede the immune system's ability to recognize and defend against such genetically "drifted" virus strains. Mismatches between vaccine strains and drifted viruses reduce vaccine effectiveness.

Nonstructural protein 1 (NS1) is produced by influenza viruses in infected cells to counter the host immune response. NS1 blocks interferon, a key component of the immune system's response to viral infection. deltaFLU is composed of influenza vaccine strains genetically modified by deletion of the NS1 gene. Lacking NS1, deltaFLU induces high levels of interferon, achieving a natural adjuvant effect that stimulates cell-mediated and antibody-mediated immunity. deltaFLU strains are replication-deficient, which makes the vaccine safe. Thus, deletion of NS1 achieves two important properties: 1) attenuation, and 2) robust, cross-protective immunogenicity.

deltaFLU
Target Product Profile

- Broadly cross-protective
- Replication-deficient
- Self-adjuvanting
- Nasal spray administration
- Broad licensure (all ages)
- Vero cell-based manufacture

Broad cross-protection against unmatched influenza strains, and antibodies that cross-neutralize drifted strains, have been demonstrated in nonclinical and clinical studies of deltaFLU. Volunteers immunized with deltaFLU produce antibodies that cross-neutralize drifted strains and even cross-neutralize strains of different subtypes. In a nonclinical study, deltaFLU provided cross-protection against antigenically drifted strains as well as a shifted strain containing a completely different HA protein. These clinical and nonclinical data demonstrating protective mechanisms against a broad range of influenza A and B strains are strong indicators of the potential of deltaFLU as a universal seasonal influenza vaccine.



Administered as a nasal spray, deltaFLU elicits broadly cross-neutralizing antibodies in the nasal mucous membranes, generating a first line of defense directly at the point of entry of circulating viruses. Nasal spray administration is simple and pain-free, and circumvents the hazards of needle stick and needle disposal inherent with conventional influenza vaccines.

Completed clinical trials show that deltaFLU is safe, immunogenic, and generates vaccine-specific mucosal and serum antibodies to homologous and heterologous influenza strains (i.e., cross-neutralizing antibodies) in a dose-dependent manner. deltaFLU candidate vaccines for seasonal and pandemic influenza have been evaluated in a total of four Phase 1 and 2 clinical trials enrolling 245 healthy adults.

Manufacture of deltaFLU in Vero cells provides significant advantages over traditional egg-based manufacture of influenza vaccines in terms of speed, capacity, reliability, and cost. Vivaldi has developed a high-efficiency, high-yield Vero cell production process for deltaFLU vaccines that is readily scalable. The process takes only 12 weeks from strain selection to product release for clinical use. Traditional egg-based production of influenza vaccines takes up to 6 months, and may induce antigenic changes that reduce vaccine efficacy.

Seasonal influenza is a serious disease and a significant public health problem. Worldwide, one billion cases of seasonal influenza and up to 500,000 influenza-related deaths occur annually. Each year 5-20% of the US population contracts influenza, leading to as many as 226,000 hospitalizations and 36,000 deaths. Increased awareness of the need for vaccination against influenza, broader recommendations for vaccination, and aging populations are fueling growth in the world market for seasonal influenza vaccines, valued at over $5 billion.

Focus on Pediatric Influenza

- Children are the main reservoir and vector
- Incidence of influenza is >2x that of adults
- 90 million cases / year worldwide in children <5 years
- 20,000 hospitalizations / year in US children < 5 years
- Children < 2 years are at greatest risk of severe disease
- Recommendations for universal pediatric influenza immunization are increasing

Vivaldi's goal is to develop a deltaFLU influenza vaccine licensed for all age groups, including children as young as 6 months and elderly adults. Vivaldi has developed detailed plans for an 18-month Phase 2 program in the EU that will enroll adults and children. Pediatrics presents unique unmet needs and strong near-term market growth potential. Addressing the pediatric market with a safe and effective vaccine is a high priority for the pharmaceutical industry. Vivaldi plans to undertake late-stage development and commercialization of deltaFLU through a partnership or license.

deltaFLU Advantages for Pandemic Preparedness

- Rapid response to emerging strains using reverse genetics and plasmid rescue
- Dose-sparing, without requiring adjuvant
- Nasal spray dosage form amenable to self-administration and mass use

Pandemic influenza is a relentless global public health threat. Three influenza pandemics in the 20th century caused over 50 million deaths in total. The 2009 H1N1 influenza pandemic led to over a quarter of a million deaths worldwide. Governments and international health organizations have prioritized and budgeted significant funding for development of vaccines for pandemic preparedness. Vivaldi successfully completed a Cooperative Research and Development Agreement (CRADA) with the National Institute of Allergy and Infectious Diseases for preclinical development of a vaccine candidate against a strain with pandemic potential. The company is seeking additional government support for clinical development of deltaFLU candidates for seasonal and pandemic influenza.

Vivaldi's management team has significant experience in the pharmaceutical industry, and expertise in virology, immunology, and influenza vaccine development and production. Vivaldi's co-founders Drs. Peter Palese and Adolfo García-Sastre at the Icahn School of Medicine at Mount Sinai are pioneers in the fields of influenza genomics and NS1. They support Vivaldi on an ongoing basis as scientific advisors. The company has raised over $36 million in institutional venture capital, led by NGN Capital. Vivaldi is headquartered in Fort Collins, Colorado; its European affiliate Vivaldi Biosciences AG is located in Vienna, Austria.

Management and Directors	Affiliations / Experience
William Wick, MBA, *CEO*	Lumendi, Vision Capital, ZoZa, National City Corporation
Thomas Muster, PhD, *CSO*	Blue Sky Vaccines, AVIR Green Hills
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John Costantino, JD, *Chairman*	NGN Capital, Walden, Conair, Touche Ross
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