WHITE PAPER

Boosting mRNA: Mucosal Immunity and a Platform beyond it

Adding a Mucosal Booster Layer to Established Respiratory Vaccine Franchises

AdJane

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Executive Summary

mRNA vaccines transformed respiratory disease prevention but, like other intramuscular vaccines, leave a recognized gap at the mucosal site where respiratory pathogens initiate infection. AdJane Biosciences ("AdJane") has developed a new mucosal booster concept designed to close this gap: an intranasal *Neisseria meningitidis* native Outer Membrane Vesicle ("Nm-nOMV") booster, administered after intramuscular priming, that adds mucosal immunity at the site of infection without disrupting established immunization programs.

AdJane's recently completed Phase 1 study – published in *Vaccines* in June[1] – provides the first clinical evidence supporting the concept. Within the study, an identified subset of participants who had been primed with Pfizer or Moderna mRNA COVID-19 vaccines received the intranasal Nm-nOMV + SARS-CoV-2 Spike booster. Across the mRNA-primed individuals, the booster was safe and induced significant mucosal IgA responses, with indications of progressive immune maturation through Day 64.

AdJane sees clear potential for the same intranasal booster approach beyond mRNA. Because the mucosal gap is prevalent across all intramuscular respiratory vaccines, a booster that complements one priming platform could also complement others. AdJane has filed a patent covering the broader use of Nm-nOMVs as a mucosal booster for respiratory vaccines.

Underlying the concept is a clinically deployable platform. AdJane's vesicles are derived from *Neisseria meningitidis* , the only bacterial species from which outer membrane vesicles have reached the market: GSK's Bexsero (4CMenB), an intramuscular vaccine approved by both FDA and EMA. That precedent establishes regulatory and manufacturing familiarity with Nm-OMVs as a vaccine component, from which AdJane has developed its own proprietary Nm-nOMV platform. The platform has proven GMP manufacturability and scalability, stability for at least 2.5-years at standard refrigeration, and is covered by layered IP extending beyond 2045. Importantly, the platform has been independently assessed by public health and commercial collaborators such as CARB-X, CEPI and CDBIO.

[1] Kraan, H.; van der Geest, A.; Oosterhoff, D.; Kruiswijk, C.; Soema, P. A Randomized, Double-Blind, Placebo-Controlled Phase I Study to Evaluate the Safety, Tolerability, and Immunogenicity of an Outer Membrane Vesicle (OMV) Platform-Based Vaccine Administered Intranasally to Healthy Adults. *Vaccines* 2026, 14, 575. https://doi.org/10.3390/vaccines14070575

SECTION 01

1. The Mucosal Gap and the Booster Concept

The gap left by intramuscular respiratory vaccines

Approved respiratory vaccines – mRNA, recombinant protein, and conjugate formulations – are administered intramuscularly and primarily elicit systemic immunity: strong serum IgG, neutralizing antibodies, and effective protection against severe disease. Respiratory pathogens, however, enter the body at mucosal surfaces. The limited nasal IgA induced by intramuscular vaccines helps explain clinically important observations such as limited transmission reduction even in well-vaccinated populations and vulnerability to breakthrough infections with antigenic drift.

Public health authorities have increasingly identified reduction of infection and transmission, rather than severe disease alone, as a priority for next-generation respiratory vaccines. Closing the mucosal gap has nonetheless proven technically difficult. Live attenuated approaches carry use restrictions; recombinant and nanoparticle mucosal candidates remain largely in early-stage development. The dominant intramuscular platforms, including the mRNA vaccines, drive strong systemic immunity but induce little mucosal IgA. No mucosal complement to the dominant intramuscular respiratory vaccines has yet been broadly deployed.

Mucosal Booster

Rather than developing a stand-alone mucosal vaccine that would compete with established intramuscular vaccines, AdJane proposes a mucosal booster designed to complement them. The booster is administered intranasally to individuals already carrying systemic immunity from prior intramuscular vaccination, adding mucosal IgA at the site of infection without disrupting existing immunization schedules.

DIMENSION	EXISTING IM RESPIRATORY VACCINES	INTRANASAL NM-NOMV BOOSTER
Systemic immunity	Strong serum IgG, neutralizing antibodies	Complements existing systemic response
Mucosal immunity	Limited nasal IgA induction	Adds mucosal IgA at site of infection
Site of action	After systemic infection establishes	At respiratory entry point
Existing programs	Established globally	Complementary – no disruption required
Cold chain	Ultra-cold-chain (mRNA) or standard refrigeration (2-8°C)	Standard refrigeration (2-8°C)
Administration	Injection	Needle-free intranasal

Why the concept is distinctive

01 **Commercially complementary:** The booster adds value to existing intramuscular respiratory vaccine franchises rather than displacing them, aligning incentives with the established vaccine industry.

02 **Platform-agnostic in principle:** The concept does not depend on a specific priming platform. mRNA, recombinant protein, or conjugate priming should each be compatible, subject to validation.

03 **Compatible with existing schedules:** Periodic intranasal boosting can integrate into established annual or seasonal vaccination programs.

04 **Large addressable population already vaccinated:** Several billion respiratory vaccine doses have been administered globally. The population with prior systemic immunity is large and growing.

SECTION 02

2. Phase 1 Clinical Evidence: The mRNA-Primed Subset

AdJane's recently completed Phase 1 study provides the first clinical evidence supporting the booster concept. The study was a randomized, double-blind, placebo- and OMV-controlled Phase 1 trial in 40 healthy adults, evaluating two escalating doses of intranasal Nm-nOMV + SARS-CoV-2 Spike on Day 1 and Day 22, with follow-up through Day 64.

An identified mRNA-primed subset within the study

Within the Phase 1 cohort, an identified subset of participants had received prior Pfizer (Comirnaty, majority) and/or Moderna (Spikevax) mRNA COVID-19 vaccination before entering the study. [2] This subset is directly relevant to the booster concept: it represents the population for whom a mucosal booster would be designed – individuals with established systemic immunity from mRNA priming who would benefit from added mucosal protection at the site of infection.

[2] The mRNA-primed subset within the Phase 1 study was not pre-specified for definitive subgroup conclusions. Validation of the booster concept in mRNA-primed populations at the indication level requires dedicated Phase 2 and Phase 3 studies.

Safety in the mRNA-primed subset

- **No serious adverse events:**
  across the study population, including in the mRNA-primed subset.
- **No serious or neurological adverse events of special interest (AESIs):**
  including no Bell's palsy or other neurological signals – relevant given that intranasal boosting with an Nm-OMV-based vaccine after mRNA priming represents a novel combination.
- **Consistent safety across mRNA-primed subgroups:**
  no significant safety differences were observed between mRNA-primed and non-mRNA-primed participants.
- **Common related events were predominantly mild, local and transient:**
  oropharyngeal discomfort, nasal congestion, rhinorrhea, mild headache.

Mucosal immunogenicity in the mRNA-primed subset

- **Significant nasal IgA induction** in Pfizer-primed and Moderna-primed participants – to AdJane's knowledge, the first clinical evidence that intranasal OMV-based boosting induces mucosal immunity in mRNA-primed populations.
- **Consistent response profiles** across the two mRNA-prime subgroups, suggesting the booster effect is not specific to a single mRNA formulation.
- **Dose-dependent response** significantly increased at 14-16 days post first vaccination, 14-16 days post second vaccination, and 28-35 days post second vaccination versus the baseline, more pronounced in the higher-dose cohort.
- **Combination required for mucosal response**: no mucosal induction in OMV-only or placebo arms, indicating that the OMV + antigen combination drives the effect.

SECTION 03

3. From mRNA to a Broader Booster Category

AdJane considers it scientifically plausible that the intranasal Nm-nOMV booster approach supported by evidence in the mRNA-primed subset will be relevant to a broader category of respiratory vaccines beyond mRNA. The mucosal immunity gap is not specific to mRNA: it is shared by all dominant intramuscular respiratory vaccines, including recombinant protein and conjugate formulations. A mucosal booster that complements one intramuscular priming platform could, in principle, complement others.

Intellectual property covering the broader concept

AdJane has filed a patent covering the use of Nm-nOMV as a mucosal booster for respiratory vaccines more broadly – extending beyond the specific mRNA combination context to the general concept of intranasal Nm-nOMV boosting after intramuscular respiratory vaccination. The filing reflects AdJane's view that the booster concept represents a category of respiratory vaccine technology, not a single product application.

Potential application contexts

Subject to dedicated clinical validation in each context, the booster concept may be relevant for:

- Annual COVID-19 boosting in mRNA-primed populations - the application directly supported by the Phase 1 mRNA-primed subset
- Seasonal influenza vaccination programs seeking enhanced infection and transmission control
- RSV vaccination programs developing next-generation strategies
- Future combination respiratory vaccines
- Pandemic preparedness scenarios requiring rapidly deployable mucosal immunity

Continued platform development

AdJane continues to develop its platform across multiple dimensions. Beyond the heterologous prime-boost approach studied in Phase 1, AdJane sees potential in the combination of mRNA and Nm-nOMV. The company is therefore actively pursuing the development of proprietary combination methods. [3]

[3] Validation of the mucosal booster concept requires further dedicated preclinical and clinical development. The observations described in this White Paper provide initial scientific support.

SECTION 04

4. The Platform Enabling the Concept

The booster concept requires a mucosal vaccine platform that is safe, mucosally immunogenic, manufacturable at scale, distributable globally, and protected by durable intellectual property. AdJane's Nm-nOMV platform meets these requirements through a combination of features rarely seen in a clinical-stage technology.

A bacterial foundation with regulatory precedent

AdJane's platform is based on outer membrane vesicles from *Neisseria meningitidis* , the only bacterial species from which OMVs have reached the market: Bexsero (4CMenB), an intramuscular vaccine approved by both FDA and EMA.

Through Bexsero, regulators have become familiar with Nm-OMV characteristics, manufacturing and analytical methods, supported by more than a decade of population-scale safety data, as Bexsero has been administered intramuscularly to millions of individuals globally since 2013 and is incorporated into routine pediatric vaccination programs in more than 40 countries.

Built on three decades of Dutch Nm-OMV research

AdJane's Nm-nOMV platform consolidates more than 30 years of Dutch public health vaccine research from RIVM, NVI, and Intravacc – institutes that have been international pioneers in vaccinology and have contributed extensively to the field, including the initiation of the research that formed the basis for the development of the Nm-nOMV platform.

AdJane has transformed this fragmented but scientifically validated OMV technology base into an integrated platform. Through consolidation and expansion of IP, freedom-to-operate assessment, and significant investment in proprietary manufacturing and process innovations that bring the scientific foundation into operational practice, AdJane has created a platform designed for scalable pharmaceutical development of a broad range of vaccine concepts.

SECTION 04

Genetic optimization enabling flexible vaccine design

The platform is built on AdJane's genetically optimized *Neisseria meningitidis* strain, which carries four targeted gene knock-outs: together these make the vesicles safe by removing the capsule and detoxifying the LPS, increase vesicle release for higher yield, and enable multivalent antigen display. Using its proprietary methods for expressing and displaying antigens on the OMV surface, AdJane produces multivalent, self-adjuvanting OMVs that work as single-component vaccines, with antigen and adjuvant in the same particle. The same OMVs can also be mixed or coupled with separate antigens, such as recombinant proteins or T-cell epitopes. They can equally serve as a mucosal booster in individuals already primed by systemic vaccines, including mRNA, adding immunity at the body's entry points on top of existing systemic protection. The platform itself has been shown to be safe and well tolerated in a Phase 1 clinical trial, and platform-based OMVs have remained stable for more than 2.5 years under standard refrigeration. Together these options give AdJane a broad range of vaccine development strategies from a single platform.

Manufacturing innovation and distribution enabling deployment

AdJane's manufacturing process is optimized for safety, scalability, and yield. A set of proprietary innovations across fermentation and downstream processing delivers high OMV yield with fewer processing steps. These innovations could immediately be applied to both existing and next-generation OMV vaccines to provide:

- **Scalable GMP processes:**
  high productivity yield from the Nm-nOMV manufacturing process that:
  - improves batch consistency and reduces regulatory risk;
  - increases OMV yield versus conventional OMV manufacturing;
  - enables faster scale-up and supply resilience for pandemic preparedness;
  - is protected by a layered IP structure.

- **In-house GMP manufacturing capability:**
  eliminating technology transfer risk during clinical development.

- **At least 2.5 years stability at 2-8°C:**
  standard refrigeration, no ultra-cold-chain required, compatible with existing global vaccine distribution networks including low- and middle-income country (LMIC) infrastructure.

SECTION 04

Layered IP protecting the platform and the concept

AdJane has built a proprietary, layered patent estate, with **terms extending beyond 2045** , spanning the full value chain from strain to indication:

01 **Strain and production:** a genetically optimized *Neisseria meningitidis* strain with four targeted knock-outs: siaD (capsule removal for safety); lpxL1 (genetically detoxified, penta-acylated LPS); rmpM (enhanced vesiculation and yield); and porA (enabling multivalent PorA re-engineering). Produced by a detergent-free process with antifoam-enabled high-oxygen fermentation for dense growth and high yield, giving OMVs with a proprietary composition of matter.

02 **Antigen expression:** antigens genetically expressed and displayed on the Nm-nOMV through genetic engineering and lipoprotein-fusion surface display, resulting in single-component production of a multivalent vaccine.

03 **Antigen coupling:** antigens attached to the Nm-nOMV after production, linked via a conjugated linker peptide (“Click OMVs”).

04 **Adjuvant strategies:** Nm-nOMVs co-formulated with a separately produced antigen such as mRNA, recombinant protein, or others, acting as a systemic and mucosal adjuvant.

05 **Prime-boost regimens:** heterologous prime-boost, with a systemic prime followed by an Nm-nOMV mucosal booster.

06 **Therapeutic applications:** engineered lipid A variants (tetra- and hexa-acylated LPS) that tune TLR4 activation for therapeutic use, such as immuno-oncology adjuvants.

07 **Indication-specific products:** applications and products tailored to individual indications.

Patent applications and freedom-to-operate assessment are coordinated through NLO Ipsilon, with nationalization across major commercial jurisdictions.

SECTION 05

5. Independent Validation and Industry Context

CARB-X: Antimicrobial resistance

In April 2026, AdJane received a $2.6 million CARB-X award for a gonorrhea vaccine candidate, addressing a WHO high-priority pathogen. CARB-X is funded by BARDA, the Wellcome Trust, the Gates Foundation, the UK government, and other global health investors. The program validates AdJane's heterologous antigen expression capability and is scientifically supported by Bexsero's observed cross-protective effectiveness against *Neisseria gonorrhoeae* across multiple observational studies.

CEPI: Pandemic preparedness

The Nm-nOMV platform was selected as the self-adjuvanting antigen delivery system for a CEPI-supported program on the discovery of novel antigens for a broad betacoronavirus vaccine. The collaboration brings together academic, commercial and public health partners.

CDBIO: Commercial validation

AdJane's platform has also been validated commercially. Liaoning Chengda Biotechnology Co., Ltd. ("CDBIO"), a leading Chinese developer and manufacturer of human vaccines, has taken a non-exclusive license to develop a nonavalent meningococcal B vaccine (NonaMen) for the Chinese market, built on AdJane's proprietary Nm-nOMV platform. CDBIO's decision to build a product on the platform represents independent, commercial validation of the technology, complementing the scientific and public-health validation from CEPI and CARB-X.

Industry context

The global respiratory vaccine landscape spans major franchises across COVID-19, influenza, RSV, and pneumococcal indications. Several characteristics of the current environment are relevant to the booster concept: patent erosion timing across multiple respiratory franchises in the coming years, increasing public health focus on transmission control, sustained public-sector investment in pandemic preparedness through CEPI, BARDA, and the Gates Foundation, and post-pandemic emphasis on accessible cold-chain and scalable manufacturing for global deployment. Each of these elements supports the relevance of a mucosal booster category compatible with the established respiratory vaccine portfolio.

SECTION 06

6. Scientific and Strategic Perspective

Intranasal Nm-nOMV boosting represents a new category of respiratory vaccine technology – complementary to established intramuscular vaccines, compatible with existing immunization programs, and capable of addressing the mucosal immunity gap. The Phase 1 observations in the mRNA-primed subset provide initial clinical support for the concept in the mRNA context, while other preclinical findings suggest broader applicability of our Nm-nOMVs as a mucosal platform.

AdJane's boosting concept is differentiated by a number of elements: a bacterial foundation familiar to regulators, initial clinical evidence in mRNA-primed individuals, preclinical insights for broader applicability, operational maturity at a level consistent with progression through clinical development, durable IP protection covering both the current and next-generation forms of the concept, and independent assessment through CARB-X, CEPI and CDBIO collaborations.

Validation of the booster concept in specific indications will require additional, larger, clinical studies. AdJane continues to develop the platform across multiple dimensions, with additional data and program updates expected in the coming months. The platform is positioned for continued scientific development and for engagement with organizations seeking to address the mucosal immunity gap across the respiratory vaccine landscape and beyond.

IMPORTANT NOTICES

This document contains forward-looking statements subject to risks and uncertainties. Phase 1 observations do not establish definitive clinical efficacy in any specific indication; the mRNA-primed subset was not pre-specified for statistical analysis. This document is informational and does not constitute an offer to sell or solicitation of an offer to purchase any securities or financial instruments.

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