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# Viral vector vaccine for intranasal administration

Sambajog Pharmaceuticals

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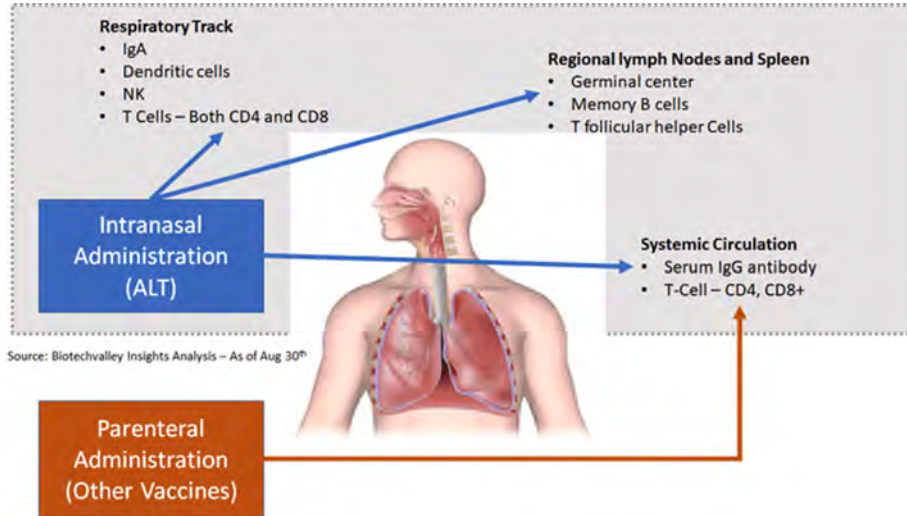
Course: Vaccines, From Concept to Implementation  
Course Directors: Philip LaRussa, MD and Lawrence Stanberry MD, PhD  
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# Viral vector vaccine for intranasal administration



- Stimulates a broad immune response including both systemic immunity (neutralizing antibody) and local immunity (mucosal IgA, resident memory T cells) in the nasal cavity and respiratory tract.

Construct



Administration



Toxicology & Immunology



Target Profile



Phase 3



Phase 4



Priority Groups

# Pros



- The only SARS-CoV2 vaccine that stimulates a local immunity. Local immunity is vital to block the viral replication of SARS-CoV2 in the nose ( the point of disease initiation and spread).

Major challenges in low income countries : Poor road network, erratic power supply, ill-equipped laboratories, storage and disposal facilities.

- Can be shipped without refrigeration directly to the patient and is able to remain temperature stable for several months.
- When refrigerated , the shelf life lasts several years.
- Being able to distribute the vaccine without requiring a cold chain makes the distribution logistics very efficient.
- Many clinics, pharmacies patent drug stores lack ultra-low temperature freezers in these regions. Since our vaccines does not require these, there is onsite availability of the vaccine at major healthcare facilities.

Construct



Administration



Toxicology &  
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Target Profile



Phase 3



Phase 4



Priority Groups

# Cons

- The concept of intranasal vaccines are new and there are not many studies that have been conducted in the past when compared to their oral and intramuscular counterparts.
- Possible long term adverse reactions

Construct



Administration



Toxicology &  
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Target Profile



Phase 3



Phase 4



Priority Groups

# Route of administration ; PROS



- Rapid, safe, non-invasive method.
- Simple, nasal delivery ; does not require needles (The prevalence of blood borne diseases e.g HIV in some low income countries is considerably high and some clinics do not have adequate disposal facilities for needles and hazardous wastes ; our construct does not require needles thus takes care of risk of infection via needles)
- Single dose.
- Packaged with a self contained nasal spray with ease of deployment and administration.
- Can be self administered
- Rapid absorption due to highly vascularized nasal mucosa.

# Route of administration ; CONS



- Rapid elimination of substance from nasal cavity due to mucociliary clearance.
- Nasal congestion due to cold/allergies may interfere with the technique of delivery.
- Only a limited volume can be sprayed into the nasal cavity.
- Frequent use can cause mucosal damage/irritation (Hence we minimize the number of doses:single dose)
- Mechanical loss of dosage form is possible if technique is not proper.
- Intranasal administration may be inconvenient for some subjects.

PLATFORM	NO(se) Shot	RNA	DNA	Protein	Other Viral Vector
Expected number of doses	1	2	2	2	1-2
Route of administration	Intranasal	Injection	Injection + Electric shock	Injection	Injection
Mucosal Immunity	Yes	No	No	No	No
Stability	✓✓✓✓	✓	✓✓✓	✓✓✓	✓✓✓
Ease of Use	✓✓✓✓	✓✓✓	✓	✓✓	✓✓✓



# Preclinical toxicology

Single administration of two strains of mice by measuring the induction of spike-specific antibody levels in sera and bronchoalveolar lavage (BAL) fluids

Functionality of these vaccine-elicited antibodies will be measured in live virus neutralization assays:

We expect to see:

- Induce robust neutralizing antibody responses and mucosal IgA
- Stimulate systemic and mucosal cell-mediated immune responses characterized by T-helper 1 (Th1) type cytokine profile
- Induce cytokine producing CD4+ and CD8+ T cells, including lung-resident memory T (T<sub>rm</sub>) cells.

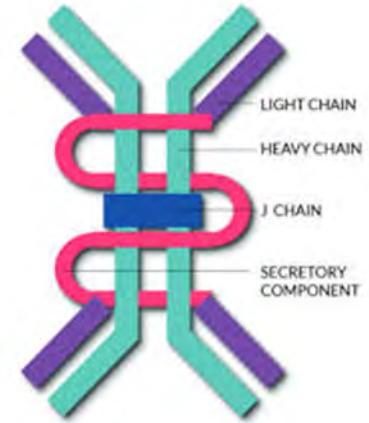
By concentrating the immune response on the RBD domain, this will decrease the production of potentially pathogenic non-neutralizing antibodies (a known driver of enhanced respiratory diseases)





# Immunology

- Neutralizing antibody responses and mucosal IgA
- Our vaccine provides two advantages over other forms of the spike antigen used in COVID-19 vaccine candidates currently in clinical development
- Expected to generate a humoral and cellular immune response in both systemic and mucosal sites, particularly within the lungs, which represent a major site for infection and clinical disease.



# Pre-clinical efficacy studies

- Nasally administered vaccines mimic a route of natural infection and is known to stimulate strong humoral and cellular immunity, both systemically and mucosally (Croyle et al., 2008).
- The intranasal route of administration has been demonstrated to bypass preexisting immunity to the vector (Croyle et al., 2008).
- Phase I trials in mice prove the efficacy and safety



# Target Product Profile

WHO Preferred Attribute (TPP)	Expected Attributes of Our Vaccine
Single dose	Seroprotection with single dose administration
Rapid onset of protection	Strong serological response at 2 weeks
Immunity lasting at least 1 year	Serological response unchanged at 400 days
Non-injected	Intranasal administration
Temperature stability	At least 3 months at 25°C in a liquid formulation
Ability to provide at low cost	High yield, scalable manufacturing process



## Enrollment Population:

- Modelled after approved COVID-19 vaccines:
  - “At least 25% (and up to 50%) of enrolled participants were to be either  $\geq 65$  years of age or 18 through  $< 65$  years of age with a protocol-defined risk factor. As of the November 11, 2020 cutoff,  $\sim 25\%$  of participants were age  $\geq 65$  years, and 16.7% of participants were age 18 to  $< 65$  years with a protocol-defined risk factor.”

*FDA Moderna VRBPAC Briefing Document 2020*

- Protocol Defined Major Risk Factor (*defined by CDC*)
  - $\geq 65$  years
  - Chronic lung disease or moderate to severe asthma
  - Serious cardiovascular conditions
  - Metabolic conditions (especially diabetes mellitus)
  - Renal failure
  - Liver disease
  - Severe obesity (BMI  $\geq 40$ )
  - Immunosuppression



# Phase 3 Trial

## Enrollment Population:

- Children/Adolescents
  - Ages 5 - 17
- Pregnant Mothers
  - “FluMist is not absorbed systemically following intranasal administration and maternal use is not expected to result in fetal exposure to the drug”
  - Phase 1 AdCovid trials did see systemic: “Systemic spike-specific IgG antibody responses in serum were detected in both strains of mice receiving a single intranasal administration of either the S1 or RBD vaccine”

**Table 3: Summary of Solicited Adverse Reactions<sup>a</sup> Observed Within 14 Days after Dose 1 for FluMist Quadrivalent and FluMist Recipients in Study MI-CP208<sup>b</sup> in Children and Adolescents 2 through 17 Years of Age**

Event	FluMist Quadrivalent	FluMist <sup>c</sup>
	N = 1341-1377 <sup>d</sup>	N = 901-920 <sup>d</sup>
Runny Nose/Nasal Congestion	32	32
Headache	13	12
Decreased Activity (Lethargy)	10	10
Sore Throat	9	10
Decreased Appetite	6	7
Muscle Aches	4	5
Fever		
> 100°F by any route	7	5
> 100 - ≤ 101°F by any route	3	2
> 101 - ≤ 102°F by any route	2	2

<sup>a</sup> Solicited adverse reactions that occurred at a higher rate ( $\geq 1\%$  rate difference after rounding) in FluMist Quadrivalent recipients compared to FluMist recipients or were identified in previous FluMist trials (see Table 2).

<sup>b</sup> NCT01091246; see [www.clinicaltrials.gov](http://www.clinicaltrials.gov)

<sup>c</sup> Represents pooled data from the two FluMist study arms [see [Clinical Studies \(14.2\)](#)].

<sup>d</sup> Number of evaluable subjects for each event.

## Inclusion groups:

- Understands and agrees to comply with the study procedures and provides written informed consent.
- High risk of SARS-CoV-2 infection - HCW, Essential, etc.
- Healthy adults or adults with pre-existing medical conditions who are in stable condition. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment.



## Exclusion groups:

- Is acutely ill or febrile 72 hours prior to or at Screening.
- Is pregnant or breastfeeding.
- Child less than 5 years old
- Known history of SARS-CoV-2 infection.
- Prior administration of an investigational coronavirus vaccine
- Known or suspected allergy or history of anaphylaxis or severe allergy to vaccine components
- Bleeding disorder considered a contraindication to intramuscular injection
- Immunosuppressive or immunodeficient state, including human immunodeficiency virus (HIV) infection, asplenia, immunosuppressants



# Phase 3 Trial

**Estimated Duration:** 9 weeks evaluation, monitored up to 2 years

- FDA recommends at LEAST a two month follow up for both safety and efficacy
- “From a ***safety perspective***, a 2-month median follow-up following completion of the full vaccination regimen will allow identification of potential adverse events that were not apparent in the immediate post vaccination period”
- “From the perspective of ***vaccine efficacy***, it is important to assess whether protection mediated by early responses has not started to wane. A 2-month median follow-up is the shortest follow-up period to achieve some confidence that any protection against COVID-19 is likely to be more than short-lived”

- FDA Moderna VRBPAC Briefing Document 2020

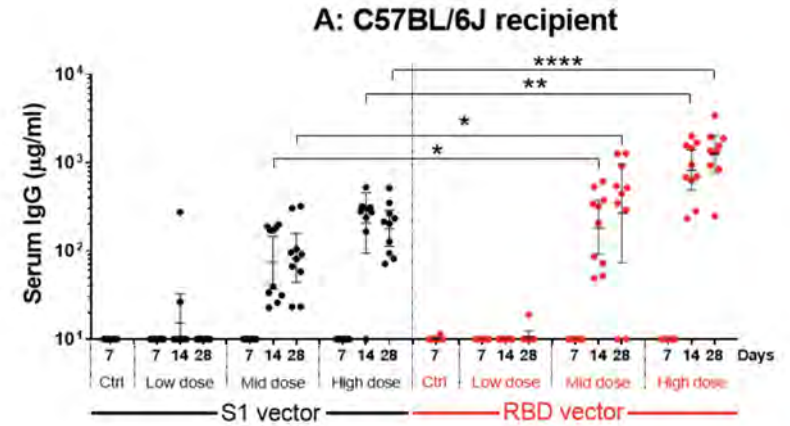
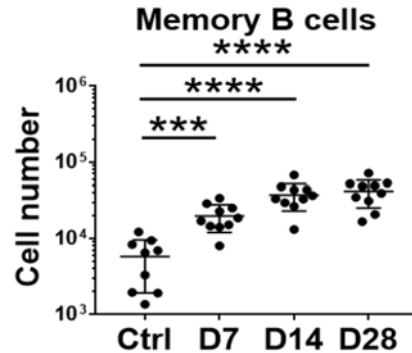
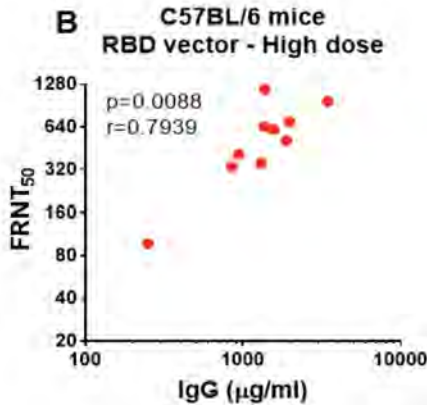




# Phase 3 Trial

## Immunization Schedule:

- Single Dose
- Altimune Preclinical Evidence
- Flumist ≈ 50% annual effectiveness



- King RG, Silva-Sanchez A, Peel JN, et al. *Single-dose intranasal administration of AdCOVID elicits systemic and mucosal immunity against SARS-CoV-2 in mice.* Preprint. *bioRxiv.* 2020;2020.10.10.331348. Published 2020 Oct 11. doi:10.1101/2020.10.10.331348

# Phase 3 Trial

## Primary Outcome Measure:

- **Pfizer-BioNtech** = “COVID-19 incidence per 1000 person-years of follow-up in participants without serological or virological evidence of past SARS-CoV-2 infection before and during vaccination regimen – cases confirmed  $\geq 7$  days after Dose 2”
- **Moderna:** “Efficacy of the vaccine to prevent protocol-defined COVID-19 occurring at least 14 days after the second dose in participants with negative SARS-CoV-2 status at baseline (i.e., negative RT-PCR and negative serology against SARS-CoV-2 nucleocapsid on Day 1).”
- **Janssen:** “The co-primary endpoints were efficacy of a single dose of vaccine to prevent centrally confirmed, moderate to severe/critical COVID-19 occurring (1) at least 14 days after vaccination and (2) at least 28 days after vaccination in study participants without evidence of prior SARSCoV-2 infection at baseline.”
- **Sambajog:** Our co-primary endpoints are (a) efficacy of the vaccine to prevent COVID-19 infection as measured by nasopharyngeal swab - PCR testing, 28 days following first (and only) dose and (b) efficacy of the vaccine to prevent moderate to severe/critical COVID-19, 28 days following vaccine.
  - Late time point: Only doing one dose so we want to prove that it can last
  - Preclinical studies show the highest IgA number, T-Helper cell, and Neutrophil counts to be at 28 days.



## Secondary Outcome Measures

- COVID-19 requiring medical intervention
- COVID-19-related death
- Any symptomatic COVID-19
- Asymptomatic COVID-19 as inferred through seroconversion
- Nasal Vaccine specific related symptoms (NVSRs)
  - Runny nose/Rhinorrhea
  - Throat irritation
  - Nasal congestion
  - Head/sinus pressure
  - Ears popping



# Phase 3 Trial

## Immunology Studies:

- Nasopharyngeal & Serum samples from all patients at 7, 14, 28 days post vaccine administration.
  - Binding antibody (bAb) concentrations for spike IgG as measured by ELISA
  - Neutralizing antibody (nAb) titers as measured by PsVNA for all dose levels at baseline and at various time points after vaccination.
  - T-cell responses as assessed by an intracellular cytokine stimulation assay.
- All participants are followed for solicited adverse reactions through 7 days post each vaccination.

## Sample Size:

- Determined based off of a power analysis of early phase trials and existing literature from J/J, Moderna, Pfizer



# Phase 4 Post-Marketing

- **Further Groups:**
  - **Pregnant Mothers**
    - “FluMist is not absorbed systemically following intranasal administration and maternal use is not expected to result in fetal exposure to the drug”
    - Phase 1 AdCovid trials did see systemic: “Systemic spike-specific IgG antibody responses in serum were detected in both strains of mice receiving a single intranasal administration of either the S1 or RBD vaccine”
  - **Children less than 5 years old**
- **Long Term Adverse Reactions (>2 years) :**
  - **Asthma**
  - **Medically Attended Events (MAE)**
    - **Any coded medical diagnosis occurring**



## Priority groups:

1. Frontline workers: Doctors, Nurses, Dentists, Hospital staff, EMS.
2. Seniors >75 yrs → Other adults between 60-75 yrs → Comorbidant patients of all ages, workers in care facilities, border protection officers at state and national level.
3. Essential workers outside the healthcare and education field: Agricultural workers, food workers, Municipal services, Disadvantaged groups, minorities, homeless people, low income migrant workers, refugees, nomadic populations.
4. Essential services: Policemen, firefighters, government officers, teachers, bankers.
5. General population