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A Mucosally-delivered Newcastle Disease Virus-vectored Booster Vaccine to Prevent SARS-CoV-2 Breakthrough Infection and Transmission

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Engineering innovative vaccines against viral pathogens by exploiting Newcastle Disease Virus

Advantages: NDV Vaccine Platform

- **No pre-existing immunity;** other APMV glycoproteins can be substituted if host immunity to NDV glycoproteins develops
- **Flexible genome** (up to 5 kb of RNA can be inserted)
- **Bilipid membrane** allows foreign antigens to be incorporated into the viral particle
  - A $1x10^9$ EID_{50} dose of live virus delivers ~8mcg purified spike protein within vaccine inoculum
- **Multiple Presentations:**
  - Inactivated v. Live attenuated
  - Intranasal v. Intramuscular
  - Monovalent, Bivalent, v. Multivalent
- **Safe and well tolerated**
- **Immunogenic**

Example of an APMV vaccine vector against Antigen X

NDV's Manufacturing and Distribution Advantages

- **Low cost of goods**
- **Grows to high titers** in embryonated chicken eggs in same facilities for manufacturing influenza vaccines
- **Simple manufacturing process,** Successfully transferred to partners in Brazil, Mexico, Thailand, and Vietnam
- **Can store inactivated formulation for at least 12 months at 2-8° C**
- **Cell line identified** for development of cell culture manufacturing process

APMV: avian paramyxoviruses

A plug-and-play **vaccine platform** to address virtually any existing or emerging viral threat

By efficiently engineering NDV to express stabilized antigenic proteins native to infectious viruses, CastleVax can develop vaccines against them. These Pandemic / Epidemic / Endemic threats include (but are not limited to):

Pipeline

- **COVID-19 (SARS-CoV-2)****
- **Respiratory Syncytial Virus (RSV)***
- **Human Metapneumovirus (HMPV)***
- **Arenaviruses (including Lassa Virus)***
- **Highly Pathogenic Avian Influenza Virus (e.g., H5N1)***

Future targets

- Filoviruses (including Ebola Virus)
- Henipaviruses
- Alphaviruses
- Rift Valley Fever Virus
- Hantavirus
- Hepatitis B Virus (HBV)
- Hepatitis C Virus (HCV)
- Cytomegalovirus (CMV)

* pre-clinical stage
** Phase 3 clinical stage

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An NDV-vectored Vaccine:

NDV-HXP-S

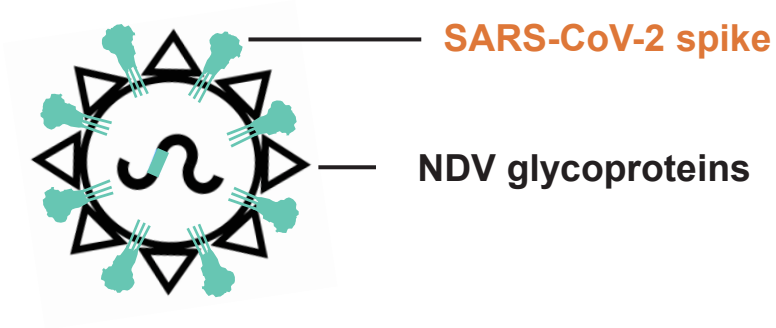
to Address SARS-CoV-2

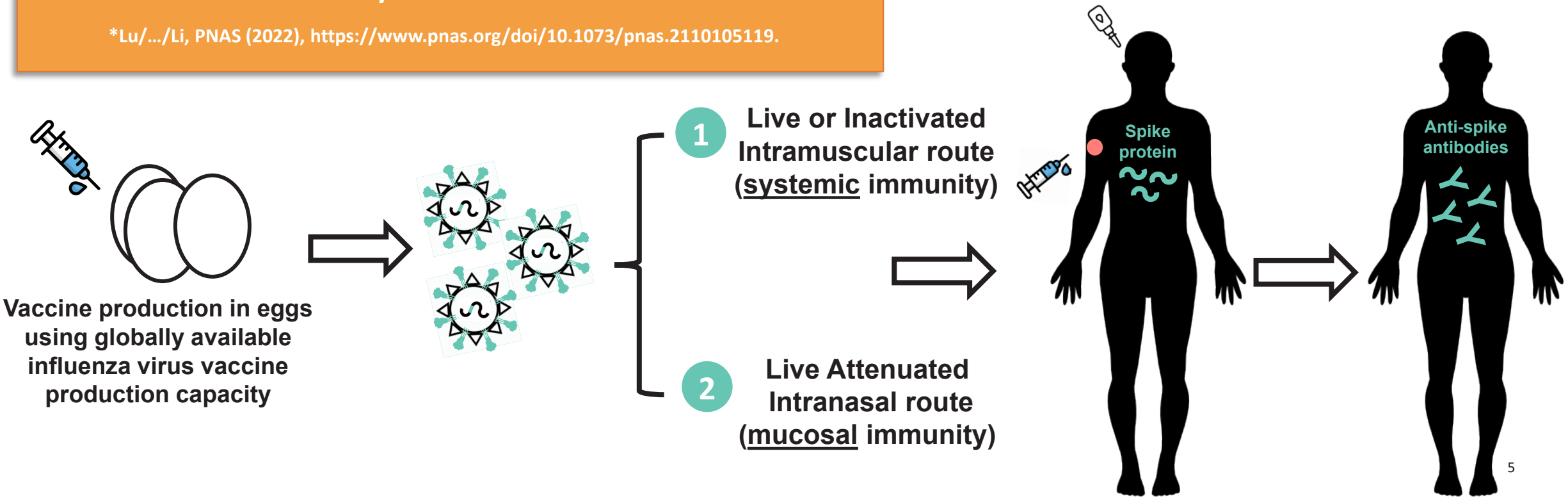
NDV-HXP-S is a late-stage SARS-CoV-2 vaccine

HXP-S refers to our Hexa-Pro (6 proline) pre-fusion conformation stabilized SARS-CoV-2 Spike protein antigen.

In animal models, the optimized HXP-S antigen is more immunogenic and protective when compared directly to early generation 2P stabilized spike proteins that are used in many currently licensed vaccines

*Lu/…/Li, PNAS (2022), https://www.pnas.org/doi/10.1073/pnas.2110105119.





Some lessons learned from the COVID-19 pandemic

Problem statements		Solutions
• Global access to the most effective vaccines has not been efficient and equitable	→	**Readily available, low-cost, global production**
• Currently licensed vaccines do not block SARS-CoV-2 infection and transmission	→	**Mucosal immunity**

An effective Pandemic Response Vaccine Platform must address these two issues

NDV can address the shortcomings of the vaccine response to the COVID-19 pandemic

1 Inequity in vaccine access

Program Goal: Provide LMICs the ability to produce their own low-cost, locally-produced systemic COVID booster vaccine

2 Lack of protection from infection and transmission

Program Goal: Develop a "next-generation" intranasal COVID booster vaccine capable of preventing breakthrough infection/transmission via mucosal immunity

Success in both of these areas will demonstrate the potential of the NDV-vectored vaccine platform to serve as an effective future pandemic response solution

LMIC partners are conducting Ph2/Ph3 clinical trials of their low-cost, locally-produced NDV-HXP-S systemic booster vaccine

Vaccine Equity

Partner	Clinical Trial Status	Total Subject Enrolled	Estimated Ph 3 Completion
GPO (Thailand)	Ph 1/2 completed Ph 2 completed Ph 3 ongoing	N=210/250 N=300 N=4,000	Q4 2023
Avi Mex (Mexico)	Ph1 completed Ph2 completed Ph 2/3 ongoing	N=90 N=158 N=400/2,168	Q4 2023
Instituto Butantan (Brazil)	Ph1 completed Ph2/3 ongoing	N=320 N=400/4,000	Q1 2025
IVAC (Vietnam)	Ph 1/2 completed	N=120/300	

Preliminary Findings:

IM delivery of the inactivated NDV-HXP-S vaccine boosts systemic immune responses equivalent to an mRNA booster and superior to a viral vector booster.

Potential for Global Production:

NDV can plug into the existing global influenza vaccine manufacturing infrastructure and support production of 3-6 billion of doses of vaccine per year and equitably meet worldwide vaccine needs.

Abbreviated Target Product Profile (TPP) for CastleVax's live virus, intranasally-delivered booster vaccine

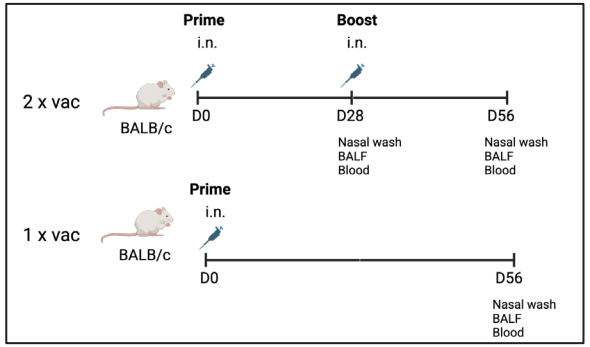
Mucosal Immunity

A single-dose, live, IN-delivered, multivalent, NDV-vectored SARS-CoV-2 booster vaccine that will effectively:

- Protect against severe disease and hospitalization caused by the circulating strains of SARS-CoV-2 (systemic immunity)

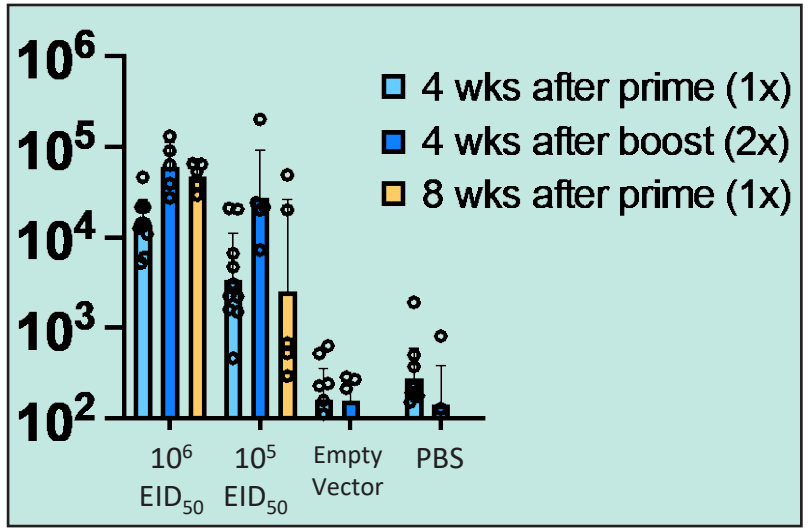
- Provide superior protection against breakthrough infection relative to existing IM administered SARS-CoV-2 booster vaccines (mucosal immunity)

Intranasal immunization of Balb/c mice with NDV-HXP-S induces systemic and mucosal immune responses

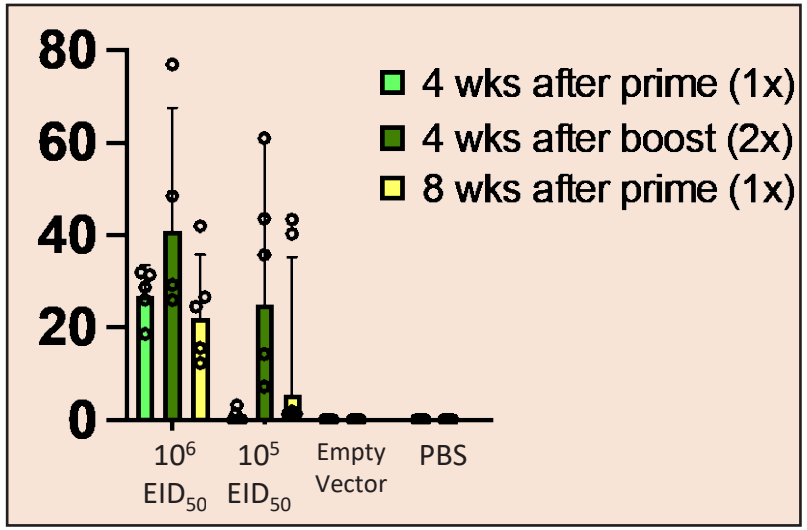


Mucosal Immunity

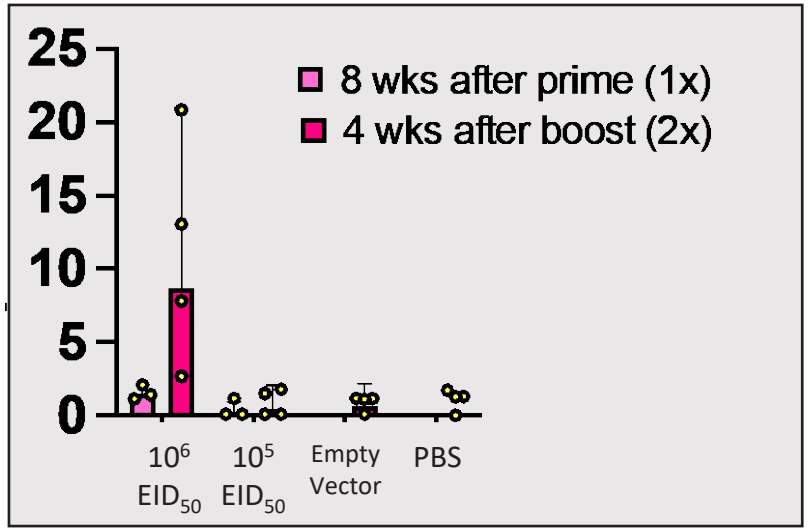
anti-S serum IgG



anti-S NW sIgA



anti-S BALF sIgA



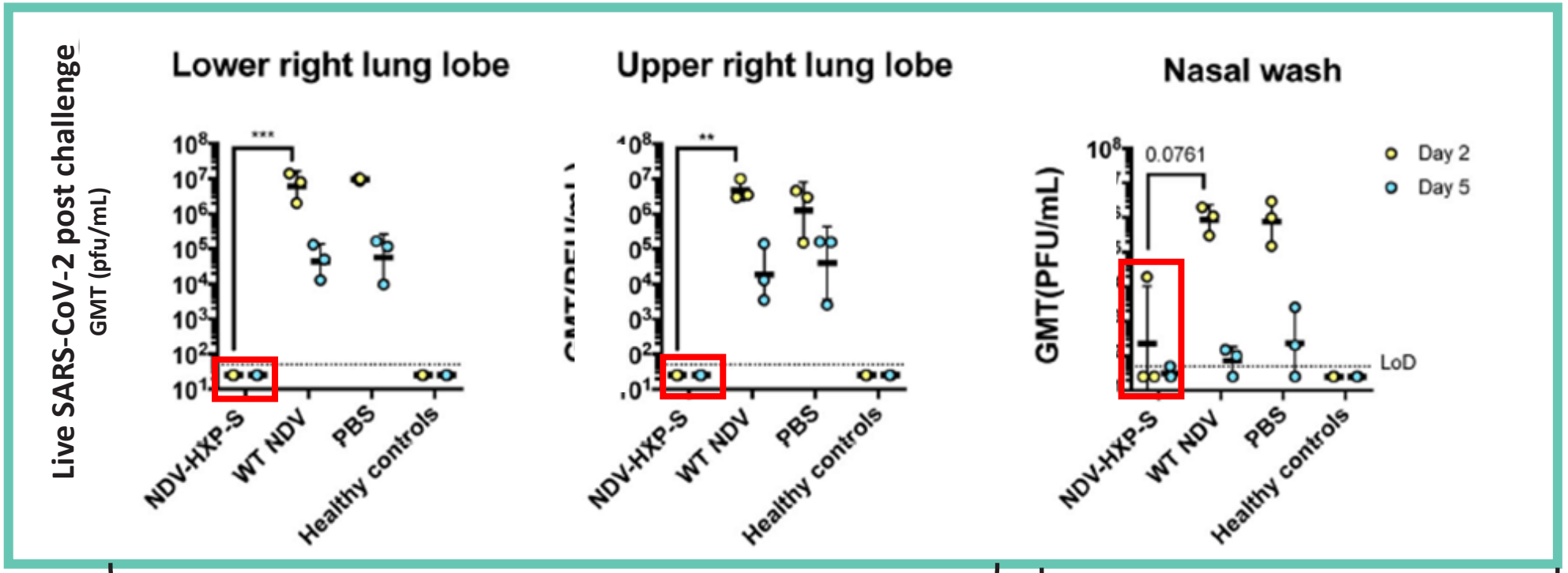
IN delivery of NDV-HXP-S induced high-titer S-specific IgG antibody responses in serum

IN delivery of NDV-HXP-S induced S-specific secretory IgA antibody responses in nasal wash (NW) and Bronchoalveolar lavage fluid (BALF)

Intranasal immunization with NDV-HXP-S protects hamsters from SARS-CoV-2 challenge

Mucosal Immunity

Group (n=6)	Immunization				Blood Draw days	Challenge (10^5 PFU)
	Vaccine	Route	Prime	Boost		
1	NDV-HXP-S	I.N.	D0	D22	D22,41	D44
2	WT NDV	I.N.	D0	D22	D22,41	D44
3	PBS	I.N.	D0	D22	D22,41	D44
4	Healthy controls	N/A	N/A	N/A	D22,41	Mock



IN delivery of NDV-HXP-S:

Prevented SARS-CoV-2 replication in the lungs

Substantially reduced SARS-CoV-2 replication in the nasal cavity

diminish the risk of virus transmission

Sun W., Nat Comm. 2021 Oct 27;12(1):6197.

We're nearing completion of our Phase 1 clinical trial

Mucosal Immunity

Phase I (NCT05181709, Mount Sinai): on-going

- 18-59 yr old, COVID vaccinated
- Single booster dose with NDV-HXP-S expressing Wuhan S

Cohort	N	D1 Vaccination Route/dose (EID_{50})	Status (as of 15Mar2023)
1	5	Placebo IN+IM	Fully Enrolled
2	5	NDV-HXP-S IN / $3.3x10^8$	Fully Enrolled
3	5	NDV-HXP-S IM / $3.3x10^8$	Fully Enrolled
DSMB Review			
4	5	NDV-HXP-S IN+IM / $6.6x10^8$	Fully Enrolled
DSMB Review			
5	5	NDV-HXP-S IN / $1.0x10^9$	Fully Enrolled
6	5	NDV-HXP-S IM / $1.0x10^9$	Fully Enrolled
DSMB Review			
7	5	NDV-HXP-S IN+IM / $2.0x10^9$	Full enrollment May2023
total	35		

1st interim data report: 28 days after the 15th person enrolled (Sept 2022)

- Overall, NDV-HXP-S appears to be safe and well tolerated
- Only 1 Grade 2 event (headache) and 2 unrelated, isolated sample handling-related, laboratory abnormalities
- No related serious adverse events

2nd interim data report (May 2023):

- 28 days after cohort 5 has enrolled

Key Immune analysis for 2nd interim report:

- Serum S/RBD-specific IgG ELISA
- Serum Wuhan neutralization titer
- Saliva S-specific IgG/SIgA ELISA titers

Ready to kick-off Phase 2 clinical trial in Q4 2023

Mucosal Immunity

Phase II: live mucosal booster vaccine

- 18 - 59 yr old, COVID vaccinated
- Single booster dose, monovalent NDV-HXP-S expressing Omicron BA.5 S
- Single booster dose, bivalent NDV-HXP-S expressing Wuhan/BA.5 S
    - vs. authorized bivalent mRNA booster vaccine

Cohort	N	D1 Vaccination Route/dose (EID_{50})	
1	10 / 2	Monovalent NDV-HXP-S-BA.5	**IN** / TBD
2	60	Bivalent NDV-HXP-S-Wuhan/BA.5	**IN** / TBD
3	60	Active Comparator: Bivalent mRNA Wuhan/BA.5	IM / TBD

Primary objectives: Demonstrate Safety

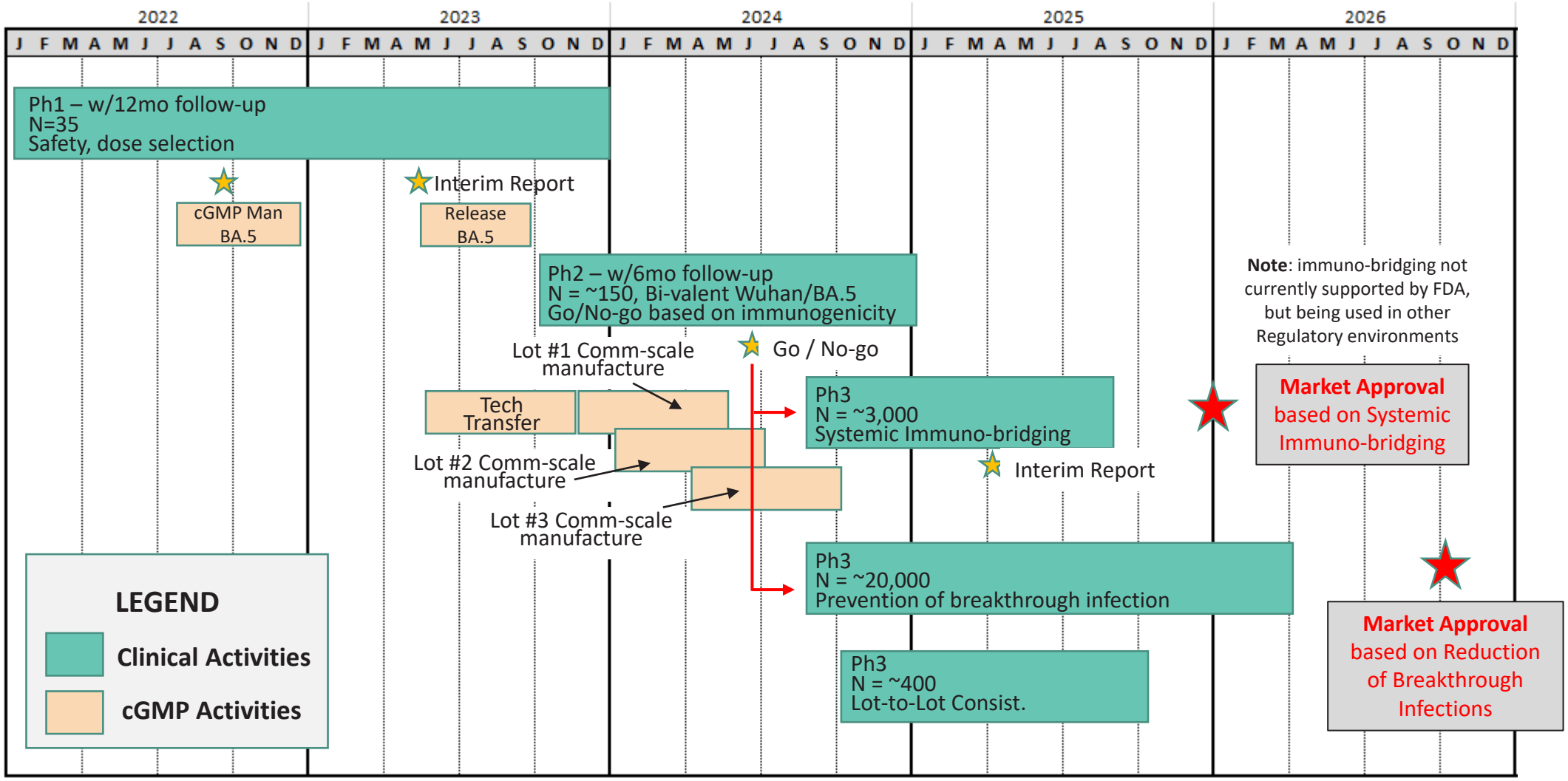
Secondary objective: Immunogenicity

- Demonstrate that mucosal delivery results in robust and high frequency mucosal immune responses
- Benchmark the ability of mucosal delivery of NDV-HXP-S to elicit mucosal and systemic immune responses relative to an active comparator vaccine delivered systemically

During a Type-C meeting conducted Feb 2023, US FDA reviewed and approved CastleVax's pre-clinical, manufacturing, clinical and regulatory strategy to advance through Phase 2

Clinical / Licensure strategy: IN delivered, live NDV-HXP-S

Mucosal Immunity



Summary

- CastleVax's LMIC partners are in **Phase 3** clinical studies with their **low-cost, locally-produced NDV-vectored systemic booster vaccine** for SARS-CoV-2.
  - Systemic administration **elicits serum neutralizing antibody responses equivalent to currently licensed mRNA vaccines** and significantly higher than ChAdOx1.
- CastleVax is in **Phase 1** with our **Intranasally (IN) delivered next-generation NDV-vectored vaccine** for SARS-CoV-2 which we believe will elicit robust mucosal immune responses necessary to protect against breakthrough infection and transmission.
- The progress we're making in the clinical development of NDV-HXP-S COVID-19 vaccine highlight the utility of **NDV as a promising pandemic response vaccine platform**:
  - **Flexible** platform allows for multiple routes of delivery/presentation; IN v. IM, inactivated v. live attenuated
  - Manufacture of NDV-vectored vaccines is simple, **low-cost** and can be easily transferred into the existing global influenza manufacturing infrastructure
  - Inactivated NDV-vectored vaccines have long-term **stability** at 4 to 8˚C
  - The **safety** data from Phase 1 and 2 studies indicate that NDV-HXP-S is well tolerated with lower reactogenicity profiles than the two approved mRNA vaccines, the Novavax protein unit vaccine, and ChAdOx1
  - No NDV pre-existing immunity in humans

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Thank You!

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