SARS-CoV-2 Protein Subunit Vaccines

A Review of Pertinent Drug Information for SARS-CoV-2

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Data as of January 27, 2021

SARS-CoV-2 Protein Subunit Vaccine Candidates

Candidate Name/Type	Sponsor	Clinical Trial Phase	Dosing	Clinical Trials
NVX-CoV2373	Novavax	Phase 3	2 doses (d0, d21)	NCT04368988 (Phase 1/2) NCT04533399 (Phase 2) EudraCT 2020-004123-16, NCT04583995 (Phase 3) NCT04611802 (Phase 3)
ZF2001 (RBD-Dimer)	Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology Chinese Academy of Sciences	Phase 3	3 doses (d0, d28, d56)	NCT04636333 (Phase 1) NCT04445194 (Phase 1) NCT04550351, ChiCTR2000035691 (Phase 1) NCT04466085 (Phase 2) ChiCTR2000040153, NCT04646590 (Phase 3)

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World Health Organization. Draft landscape of COVID-19 candidate vaccines. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. Accessed Jan. 20, 2021

Mechanism of Action | Protein Subunit

- Composed of antigens rather than the whole pathogen to elicit an antibody mediated response
  - Carefully studied to create a combination that will produce a strong response
- Most protein subunit vaccines in development require 2 doses
  - Require adjuvants for long term immunity
- Due to composition:
  - Less likely to cause adverse effects (fever, swelling at site of injection)
  - Cannot cause disease

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"Vaccine Types." National Institute of Allergy and Infectious Diseases, U.S. Department of Health and Human Services, www.niaid.nih.gov/research/vaccine-types.
Signal Transduction and Targeted Therapy (2020) 5:237. https://doi.org/10.1038/s41392-020-00352-y

Mechanism of Action | Protein Subunit

- SARS-CoV S (spike) glycoprotein
  - Popular target in vaccine development
  - Contains determinants that are known to elicit immune response
  - Responsible for receptor binding to cellular ACE2
- Other targets for SARS-CoV-2 vaccine development
  - M and N proteins
- Examples of other subunit vaccines
  - Hepatitis B
  - Acellular pertussis vaccines

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ACE2: angiotensin-converting enzyme 2

"Vaccine Types." National Institute of Allergy and Infectious Diseases, U.S. Department of Health and Human Services, www.niaid.nih.gov/research/vaccine-types.
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NVX-CoV2373 Pre-clinical and Phase I/II

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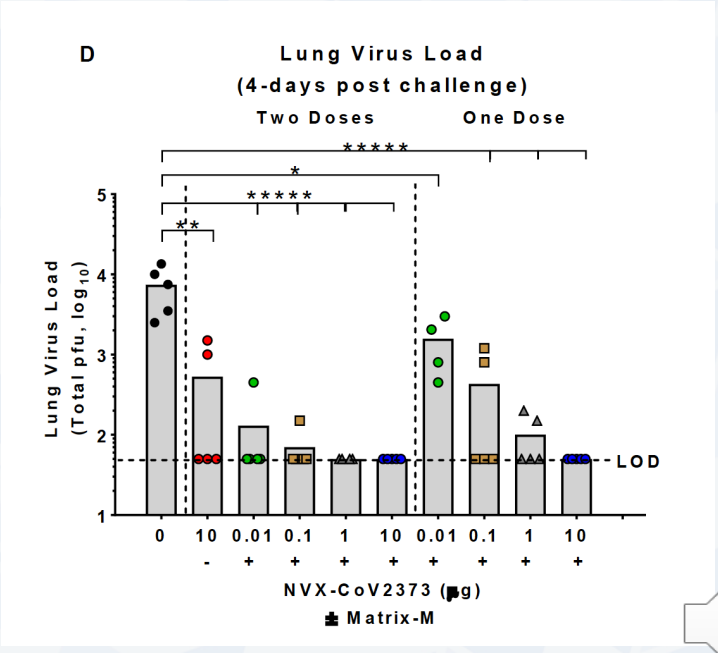
In-vivo Animal Data

Mice & olive baboons

- NVX-CoV2373: produced from full length spike (S) protein
  - Form nanoparticles that bind with high affinity to ACE2 receptor
- Studied in combination with Matrix-M adjuvant
  - Resulted in antigen specific CD4+ T cell development (Th1 dominant)
- Two dose schedule resulted in anti-S antibodies, ACE2 receptor inhibiting antibodies and neutralizing antibodies in mice and NHP
  - Mice challenged with SARS-CoV-2 that received NVX-CoV2373 with and without adjuvant had limited to no detectable viral load at day 4



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Tian et al. bioRxiv [Preprint]. 2020. https://doi.org/10.1101/2020.06.29.178509

NVX-CoV2373 (rSARS-CoV-2) Safety and Immunogenicity

- Randomized, placebo-controlled, phase 1-2 trial
  - 5-µg and 25-µg doses with or without Matrix-M adjuvant in healthy adults 60 years and younger
    - 6 participants randomized 1:1 to 5-µg and 25-µg (with adjuvant) in open-label safety assessment
    - 125 participants randomized to one of 5 vaccine groups

Vaccine Group	No. of Participants		Day 0		Day 21	
	Randomized	Sentinel	rSARS-CoV-2	Matrix-M1 adjuvant	rSARS-CoV-2	Matrix-M1 adjuvant
A	25	--	0	0	0	0
B	25	--	25 µg	0	25 µg	0
C	25	3	5 µg	50 µg	5 µg	50 µg
D	25	3	25 µg	50 µg	25 µg	50 µg
E	25	--	25 µg	50 µg	0	0

Keech et al. N Engl J Med 2020; 383:2320-2332. DOI: 10.1056/NEJMoa2026920

NVX-CoV2373 Safety and Immunogenicity

- Primary Safety Outcomes
  - Solicited local and systemic reactogenicity
    - Including duration and peak intensity for 7 days
  - Laboratory values at 7 days after vaccination
- Secondary Safety Outcomes
  - Laboratory values at day 21
  - Unsolicited adverse events during first 35 days
  - Vital signs after vaccination
  - Adverse events of special interest (SARS-CoV-2 infection, COVID-19 disease manifestations)
- Primary Immunogenicity Outcome
  - Anti-Spike IgG ELISA unit responses to rSARS-CoV-2 protein antigens

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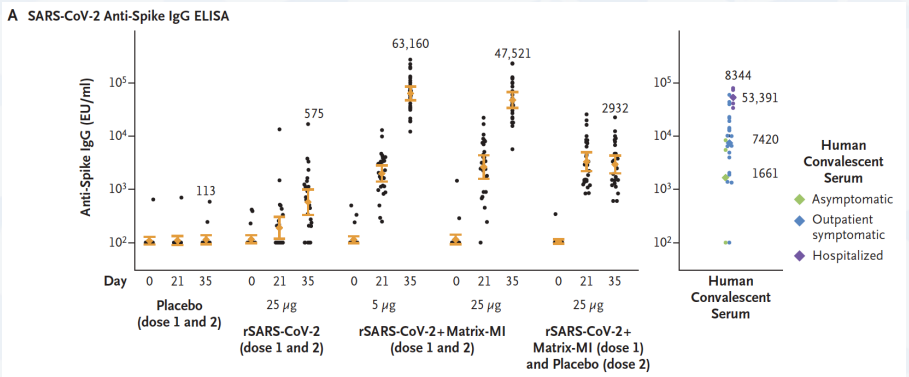
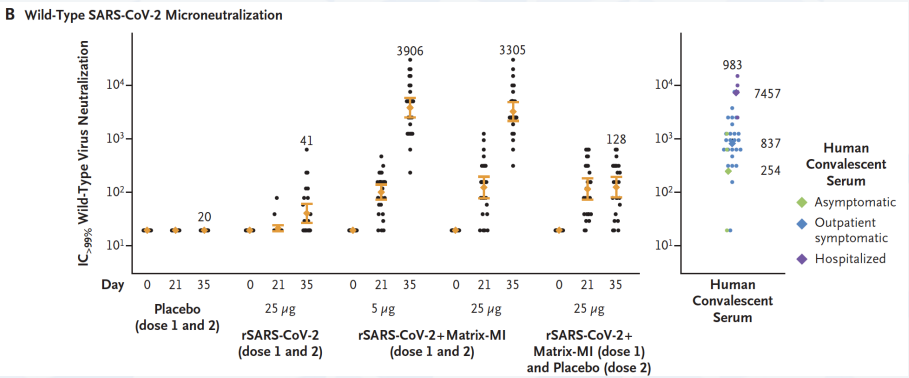
Keech et al. N Engl J Med 2020; 383:2320-2332. DOI: 10.1056/NEJMoa2026920

NVX-CoV2373

Safety and Immunogenicity

- Key Immunogenicity Findings
  - Anti-spike IgG responses occurred in all adjuvanted doses by day 21
    - Further rise seen by day 7 after second dose of adjuvant vaccines
  - Second doses of adjuvant vaccine resulted in GMEU levels that were comparable to those in convalescent serum from patients hospitalized with COVID-19
  - Neutralizing antibodies had similar response patterns after vaccination with adjuvant
  - Immune responses in the two adjuvanted regimens were similar





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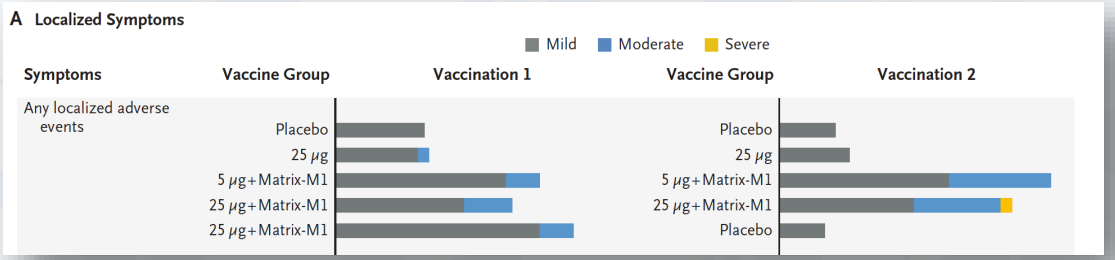
GMEU: geometric mean ELISA units

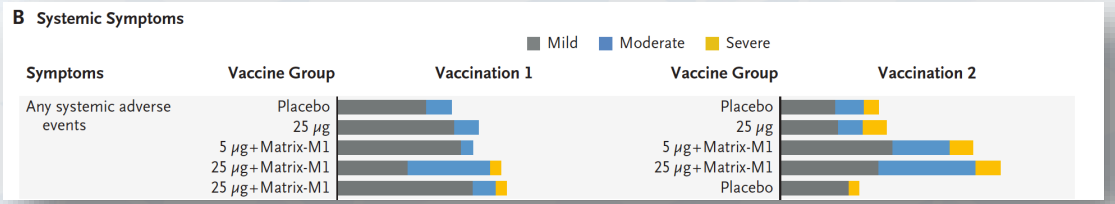
Keech et al. N Engl J Med 2020; 383:2320-2332. DOI: 10.1056/NEJMoa2026920

NVX-CoV2373

Safety and Immunogenicity

- Key Safety Findings
  - No serious adverse events or those of special interest reported
  - No severe adverse events
  - Reactogenicity absent or mild
  - Localized symptoms
    - Pain, tenderness
  - Systemic symptoms
    - Fatigue, headache, myalgia





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ZF2001 (RBD-Dimer) Phase I/II

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ZF2001 (RBD-Dimer) Safety and Immunogenicity

- Randomized, double-blind, placebo-controlled, phase 1 and 2 trials in adults 18-59 years of age
  - ZF2001: utilizes the dimeric form of receptor binding domain (RBD) as the antigen
  - Adjuvant → aluminum hydroxide
- Phase 1: 50 participants randomized to placebo, 25 µg, or 50 µg 3-dose series (30 days apart)
  - Primary Outcome – safety
  - Secondary Outcome – immunogenicity
- Phase 2: 900 participants randomized to either a 2-dose cohort or a 3-dose cohort (placebo, 25 µg, or 50 µg 30 days apart)
  - Primary Outcomes – safety and immunogenecity

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Yang et al. medRxiv [Preprint]. 2020. https://doi.org/10.1101/2020.12.20.20248602

ZF2001 (RBD-Dimer)

Safety and Immunogenicity

- Key Immunogenicity Findings
  - At day 30 after the 2nd dose, the seroconversion rates were >95% in the 2-dose group and >94% in the 3-dose group
  - At day 14 after the 3rd dose, seroconversion rates were >97% in the 3-dose group
  - Increasing the antigen from 25 µg to 50 µg did not provide significant increases in immunogenicity

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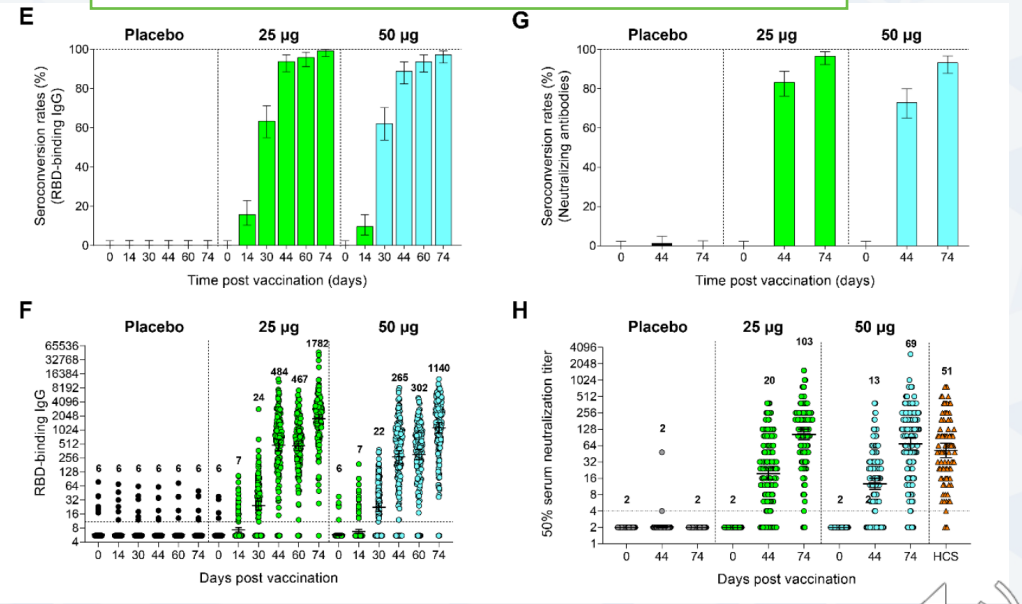
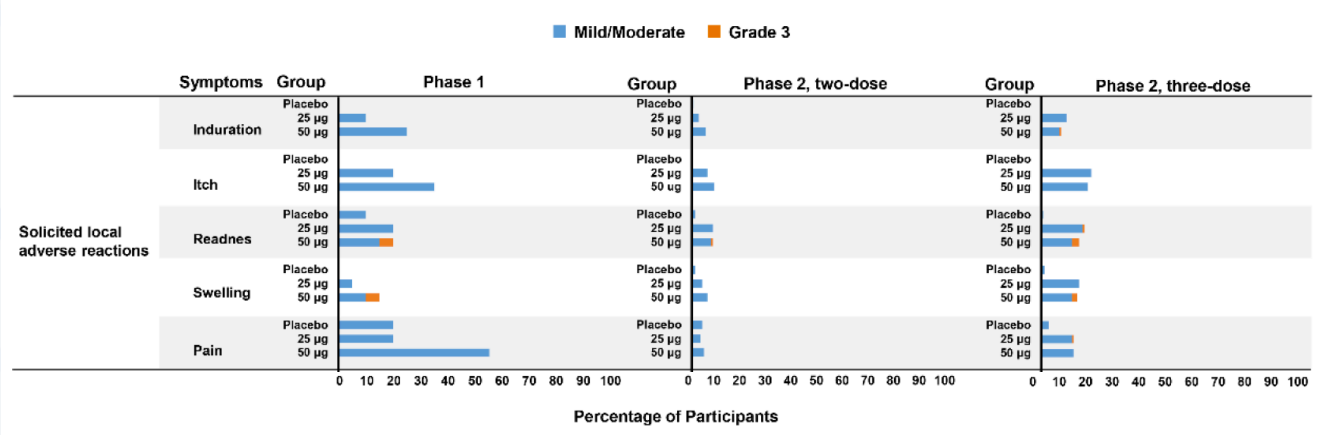
Phase Two Immunogenicity Outcome Measures



Yang et al. medRxiv [Preprint]. 2020. https://doi.org/10.1101/2020.12.20.20248602

ZF2001 (RBD-Dimer) Safety and Immunogenicity

- Key Safety Findings
  - Mild adverse reactions
    - Injection-site pain, redness, and itch
  - 7 cases of serious adverse events → not related to vaccine
  - No adverse events of special interest



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Summary

- Currently no protein subunit COVID-19 vaccines available in the U.S
- Protective effect unclear due to limited viral components in the vaccine
- Suitable for immune-compromised populations
- Lower reactogenicity and adverse events

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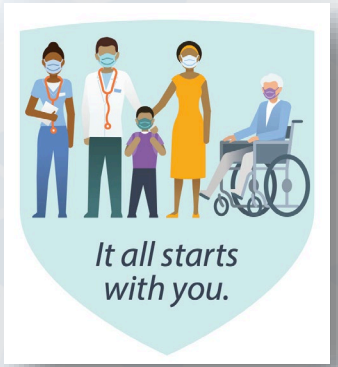
Useful Links



- CDC Website
  - https://www.cdc.gov/vaccines/covid-19/index.html
- CDC Vaccine Communication Toolkit
  - https://www.cdc.gov/vaccines/covid-19/health-systems-communication-toolkit.html
- CDC Guidance for Infection Prevention Considerations Post Vaccination
  - https://www.cdc.gov/coronavirus/2019-ncov/hcp/post-vaccine-considerations-healthcare-personnel.html
- COVID-19 Real-Time Learning Network (CDC and IDSA)
  - https://www.idsociety.org/covid-19-real-time-learning-network/

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1. Get Vaccinated
2. Tell Others Why
3. Build the Confidence

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