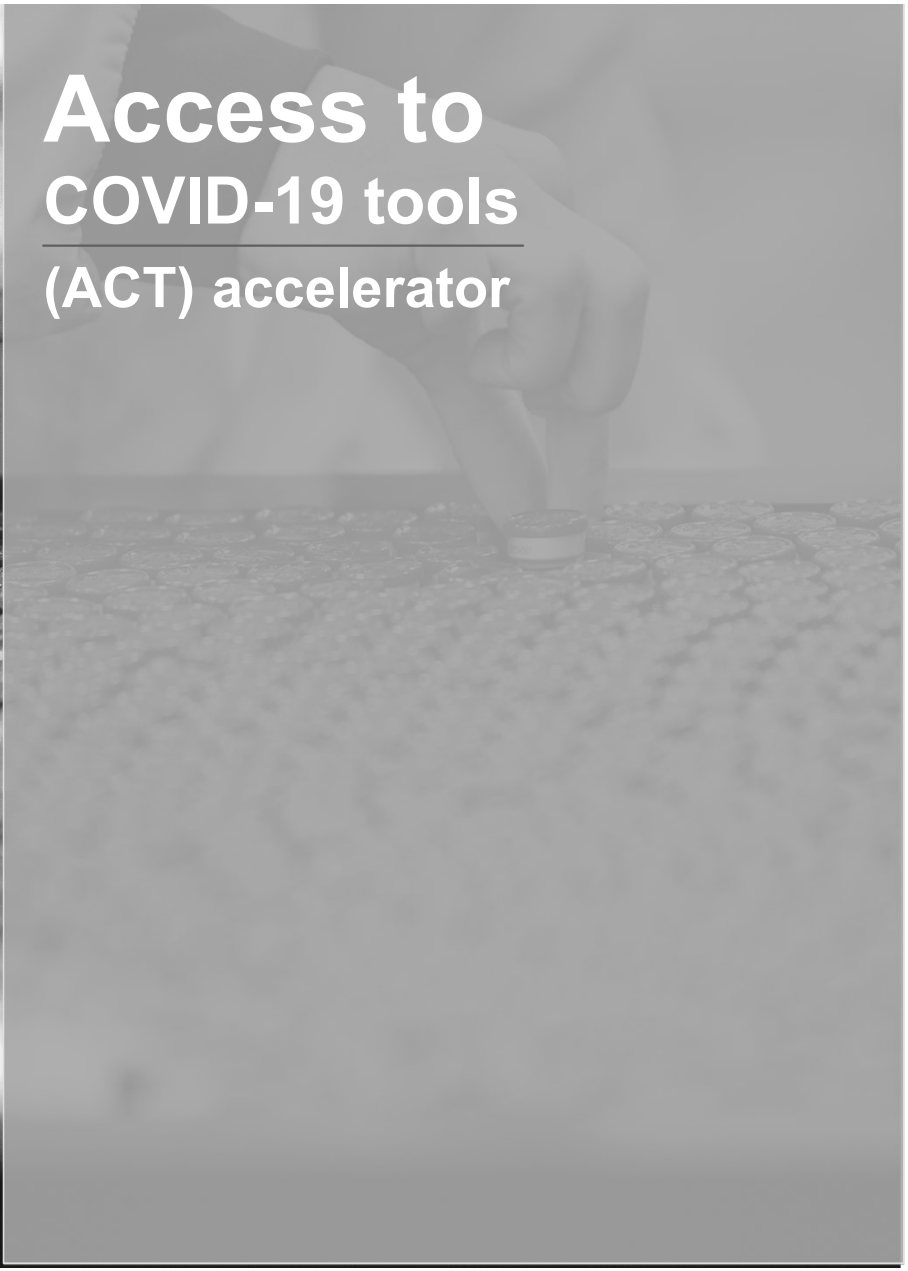
An overview of COVID vaccine clinical trial results & some challenges

DCVMN Webinar

December 8th, 2020

Access to COVID-19 tools (ACT) accelerator



ACCESS TO COVID-19 TOOLS (ACT) ACCELERATOR
A Global Collaboration to Accelerate the Development, Production and Equitable Access to New COVID-19 diagnostics, therapeutics and vaccines

DIAGNOSTICS

THERAPEUTICS

VACCINES (COVAX)

CEPI
Development & Manufacturing
Led by CEPI, with industry

Gavi
Procurement and delivery at scale
Led by Gavi

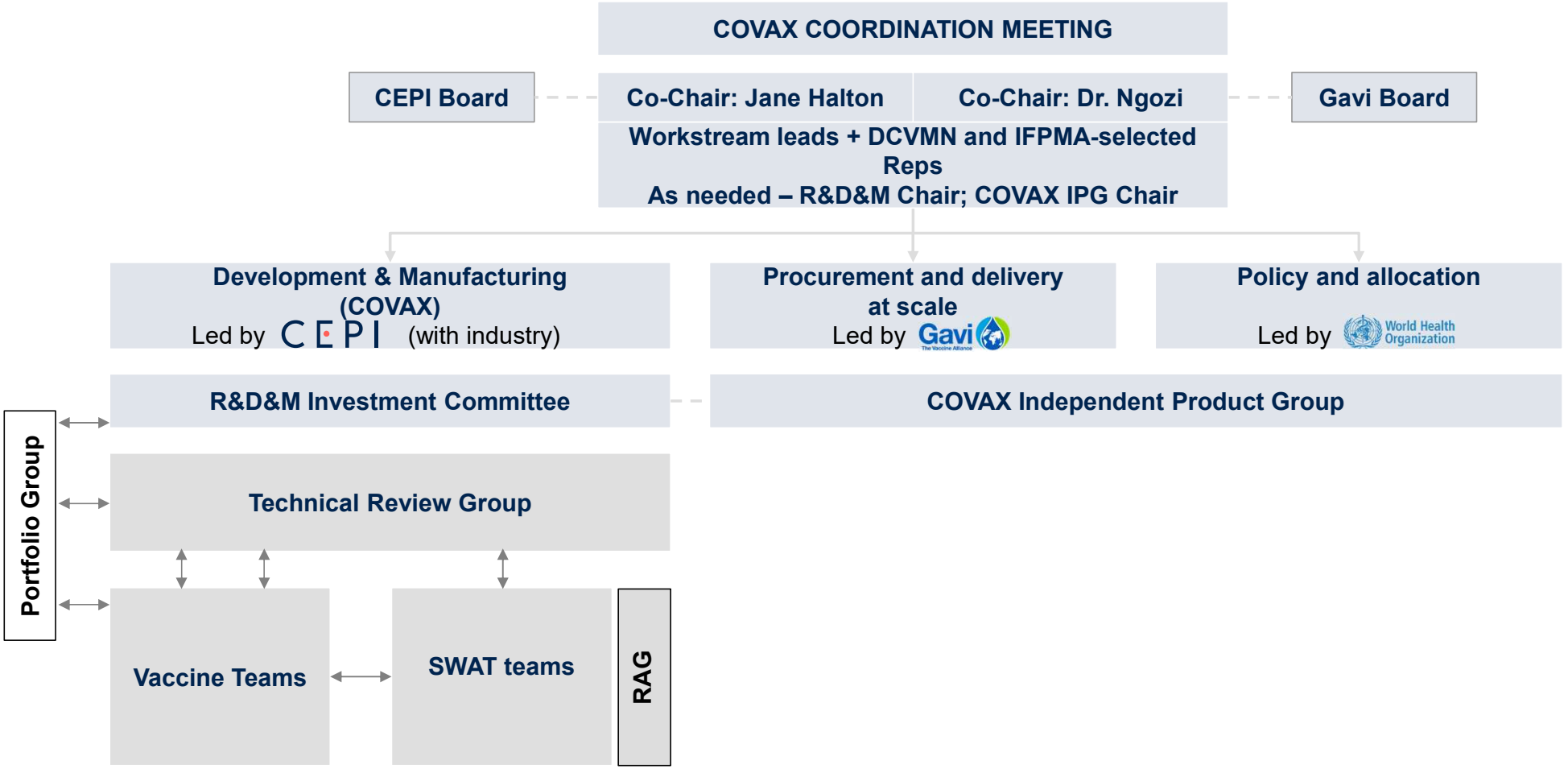
World Health Organization
Policy and allocation
Led by WHO

Key players

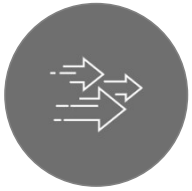
wellcome · Bill & Melinda Gates foundation · CEPI · dcvmn · Gavi · The Global Fund · IFPMA International Federation of Pharmaceutical Manufacturers & Associations · IGBA · Unitaid · World Health Organization

SOURCE: (ACT) ACCELERATOR Commitment and Call to Action 24th April 2020

ACT-A / COVAX governance



COVAX SWAT teams are being set up as a joint platform to accelerate COVID-19 Vaccine development and manufacturing by addressing common challenges together



Timely and targeted

Addresses specific cross-developer technical challenges as they are raised and/or identified on an ongoing basis

Multilateral

Establishes a dialogue and global joint effort across different COVID-19 vaccines organizations (incl. industry and other global networks)

Knowledge-based

Identifies and collates most relevant materials and insights across the broader COVID-19 ecosystem to accelerate vaccine development and manufacturing

Resource-efficient

Coordinates between different organizations/ initiatives to limit duplications and ensure expertise is efficiently leveraged

SWAT teams	Enabling sciences	Clinical Development & Operations	Manufacturing

Regulatory Advisory Group

COVAX R&D portfolio – 9 assets, 8 in clinical trials

	DNA / mRNA			Viral vectors			Protein-based		
Candidate	**Inovio** INO-4800	**Moderna** mRNA-1273	**CureVac** CVnCoV	**Merck / Themis** V591	**AstraZeneca** ChAdOx1-S	**U. of Hong Kong**	**Novavax** NVX-CoV2373	**Clover** SCB-2019	**CSL / Queensland**
Location	USA	USA	Germany	USA / Austria	UK	China	USA	China	Australia
Antigen / adjuvant	Full-length S protein	Full-length S protein	Full-length S protein	Full-length S protein	Full-length S protein	Receptor Binding Domain / AS03	Full-length S protein / saponin-based Matrix-M	Full-length S protein/AS03 or CPG1018	Full-length S protein / MF59 or AS03 or CPG1018
Current phase	Phase I/II	Phase III	Phase II	Phase I	Phase III	Pre-clinical	Phase III	Phase I	Phase I

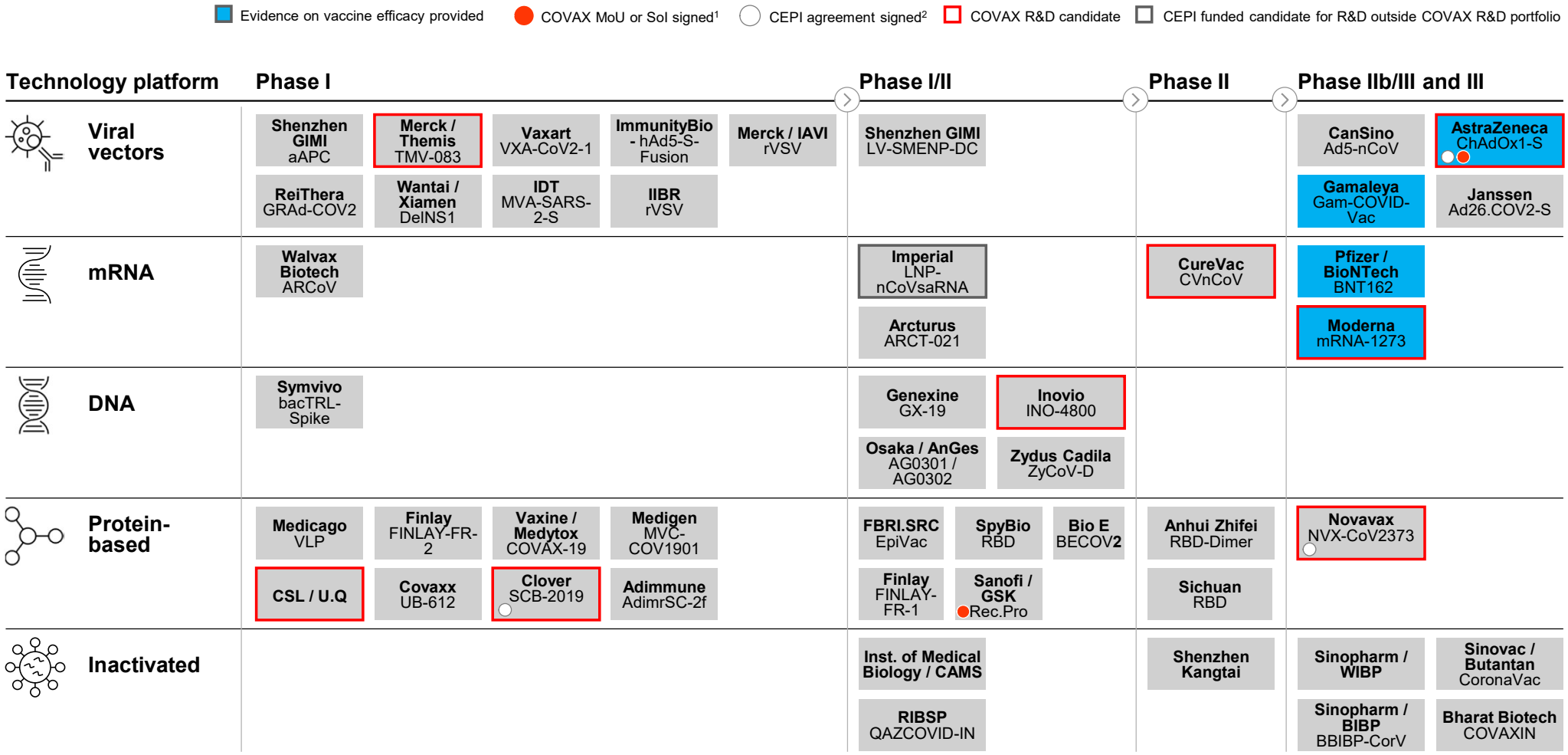
Speed

Scale

Access

UPDATED ON NOVEMBER 26, 2020

COVID-19 Vx landscape – 48 candidates in human clinical trials

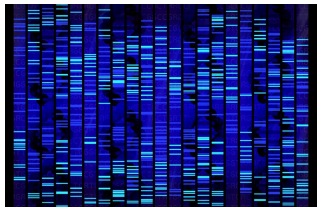


1. For advanced purchase agreement (APA); 2. For tech transfer, scale-out and reservation fees

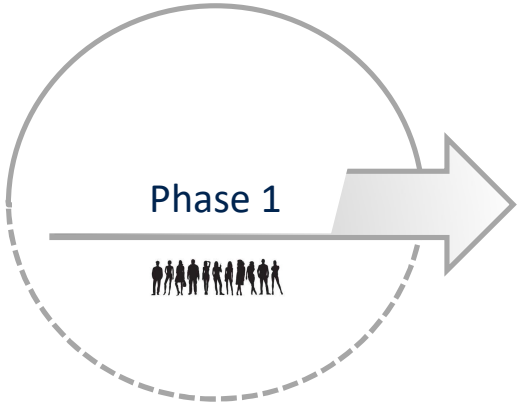
Source: CEPI Vx landscape

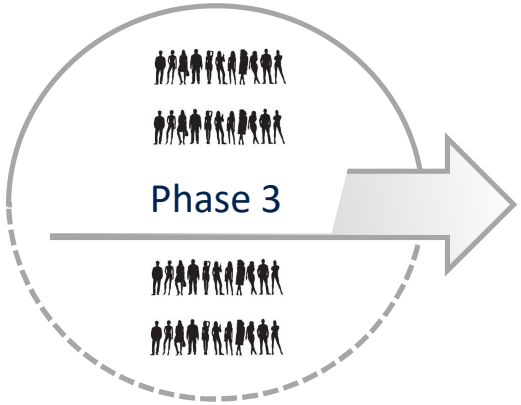
Speed: mRNA has demonstrated an unprecedented research and development pace

COVID-19 sequence release



12th January 2020





		FSFV	FSFV	1st VE IA
9 weeks	❖ Moderna	March 16th	July 27th	Nov 16th 306 days total
18 weeks	❖ Pfizer / BioNTech	May 14th	July 27th	Nov 9th 300 days total
23 weeks	❖ Curveac	June 19th		
24 weeks	❖ Imperial	June 23rd		
25 weeks	❖ Walvax	June 29th		
31 weeks	❖ Arcturus	August 11th		

→ September / October for case detection

CEPI

UPDATED ON NOVEMBER 30, 2020

Latest results from Pfizer/BioNTech, Moderna, AstraZeneca and Gamaleya

See next page

	Pfizer BioNTech	moderna	AstraZeneca / University of Oxford	The Gamaleya National Center of Epidemiology and Microbiology
Platform	mRNA (0-21 days)	mRNA (0-28 days)	ChadOx 1 vector (0-28 days ?)	Ad26 >> Ad5 prime-boost (0-21 days)
Date of press release	November 18, 2020	November 30, 2020	November 23, 2020	November 24, 2020
Preliminary point estimate of vaccine efficacy	**95% (p<0.0001)**	**94.1% (p<0.0001)**	**70% (p<=0.0001) (pooled)** **90% and 62% (LH and HH regimens[1]) (p<=0.0001)**	91.4% 28 days post dose I (7days post dose 2) Statistical significance not reported
Phase 3 study enrollment	43,661 participants to date, 41,135 of whom have received a second dose of the vaccine candidate	>30,000 participants	UK trial - 12,390 subjects, 2,742 with LH (90% efficacy) UK/Brazil trial – 10,300 HH 62% efficacy	40,000 participants 22,000 vaccinated with the first and >19,000 with second doses of the vaccine
Total number of cases	170 cases **(8 in vaccine group)** 10 severe cases (9 in placebo, 1 in vaccine group**)**	196 cases **(11 in vaccine group)** 30 severe cases (incl. 1 death), all in placebo group	131 cases across 2 trials No severe cases in vaccines	39 cases No information provided on case severity
Cold chain	-80^{0}C, 2-8^{0}C for up to 5 days	-20^{0}C, 2-8^{0}C for up to 30 days	Storage, transport and handled 2-8^{0}C for up to 6 months	2 versions: • Lyo 2-8^{0}C • Liquid Frozen -200C
Plans for licensure	• US FDA for EUA • Submitted on Dec 1st: EMA • WHO PQ	Submitted on Nov 30th: EUA with US FDA and EMA conditional marketing authorisation	EMA, MHRA, PQ	Emergency authorization in Russia Plan for global license

1 LH – Low dose followed by High dose, HH – 2 doses of high dose formulation

UPDATED ON NOVEMBER 30, 2020

Deep dive AstraZeneca candidate

Pfizer/ BioNTech

Moderna

AstraZeneca/ Univ. o. Oxford

Gamaleya Institute

Evaluation of current data/approach/…
Interim analysis: Pooled data from the UK and Brazilian trials.

Implications on other technology platforms/ candidates
Together with Gamaleya (Ad36 >> Ad5) first results on a viral vector vaccine platform (2-dose regimen). Oxford / AZ vaccine regimen based on ChAdOx-1 for both, 1st and 2nd dose.

Next steps/missing information

Data

- Precise VE point estimates with 95% CIs (overlap of lo-hi and hi-hi VE confidence intervals?)
- Trial group-specific immunogenicity (nAbs, ELISA, CMI)
- Influence of anti-vector immunity?
- Correlation of immune response and vaccine efficacy over time
- Stratified data (by trial / country, by age group, immunization schedule etc.) with respective 95% CIs
- Confirmative data from other Oxford / AZ trials, in particular the RSA trial as well as the Ph3 trial in the USA
- PCR results re asymptomatic infection → protection against infection?

Manufacturing

- Understand manufacturing: Oxford CTM facility versus CMO

based on 94 cases (IA):

- Placebo: 86
- Vaccine: 8

based on 2nd 76 cases:

- Placebo: 76
- Vaccine: 0

based on all 170 cases:

- Placebo: 162
- Vaccine: 8

BIONTECH

Pfizer and BioNTech Conclude Phase 3 Study of COVID-19 Vaccine Candidate, Meeting All Primary Efficacy Endpoints

November 18, 2020

- *Primary efficacy analysis demonstrates BNT162b2 to be 95% effective against COVID-19 beginning 28 days after the first dose; 170 confirmed cases of COVID-19 were evaluated, with 162 observed in the placebo group versus 8 in the vaccine group*
- *Efficacy was consistent across age, gender, race and ethnicity demographics; observed efficacy in adults over 65 years of age was over 94%*
- *Safety data milestone required by U.S. Food and Drug Administration (FDA) for Emergency Use Authorization (EUA) has been achieved*
- *Data demonstrates vaccine was well tolerated across all populations with over 43,000 participants enrolled; no serious safety concerns observed; the only Grade 3 adverse event greater than 2% in frequency was fatigue at 3.8% and headache at 2.0%*
- *Companies plan to submit within days to the FDA for EUA and share data with other regulatory agencies around the globe*
- *The companies expect to produce globally up to 50 million vaccine doses in 2020 and up to 1.3 billion doses by the end of 2021*

NEW YORK and MAINZ, GERMANY, November 18, 2020 —Pfizer Inc. (NYSE: PFE) and BioNTech SE (Nasdaq: BNTX) today announced that, after conducting the final efficacy analysis in their ongoing Phase 3 study, their mRNA-based COVID-19 vaccine candidate, BNT162b2, met all of the study's primary efficacy endpoints. Analysis of the data indicates a vaccine efficacy rate of 95% ($p<0.0001$) in participants without prior SARS-CoV-2 infection (first primary objective) and also in participants with and without prior SARS-CoV-2 infection (second primary objective), in each case measured from 28 days after the first dose, 7 days after the second dose. The first primary objective analysis is based on 170 cases of COVID-19, as specified in the study protocol, of which 162 cases of COVID-19 were observed in the placebo group versus 8 cases in the BNT162b2 group. Efficacy was consistent across age, gender, race and ethnicity demographics. The observed efficacy in adults over 65 years of age was over 94%.

There were 10 severe cases of COVID-19 observed in the trial, with nine of the cases occurring in the placebo group and one in the BNT162b2 vaccinated group. To date, the Data Monitoring Committee for the study has not reported any serious safety concerns related to the vaccine. A review of unblinded reactogenicity data from the final analysis which consisted of a randomized subset of at least 8,000 participants 18 years and older in the Phase 2/3 study demonstrates that the vaccine was well tolerated, with most solicited adverse events resolving shortly after vaccination. The only Grade 3 (severe) solicited adverse events greater than or equal to 2% in frequency after the first or second dose were fatigue at 3.8% and headache at 2.0% following dose 2. Consistent with earlier shared results, older adults tended to report fewer and milder solicited adverse events following vaccination.

[https://investors.biontech.de/node/8771/pdf, published 18th November 2020]

Moderna, November 30th, 2020

EMBARGOED UNTIL MON., NOVEMBER 30 AT 7:00 AM EST / 12:00 PM GMT

Moderna Announces Primary Efficacy Analysis in Phase 3 COVE Study for Its COVID-19 Vaccine Candidate and Filing Today with U.S. FDA for Emergency Use Authorization

Primary efficacy analysis of the Phase 3 COVE study of mRNA-1273 involving 30,000 participants included 196 cases of COVID-19, of which 30 cases were severe

Vaccine efficacy against COVID-19 was 94.1%; vaccine efficacy against severe COVID-19 was 100%

mRNA-1273 continues to be generally well tolerated; no serious safety concerns identified to date

Phase 3 COVE Study has exceeded 2 months of median follow-up post vaccination as required by the U.S. FDA for Emergency Use Authorization (EUA)

Moderna plans today to request EUA from the U.S. FDA, to apply for a conditional marketing authorization with the European Medicines Agency (EMA) and to progress with the rolling reviews, which have already been initiated with international regulatory agencies

FDA has told Company to expect VRBPAC meeting for mRNA-1273 likely on December 17, 2020

CAMBRIDGE, Mass.—November 30, 2020 – Moderna, Inc. (Nasdaq: MRNA), a biotechnology company pioneering messenger RNA (mRNA) therapeutics and vaccines to create a new generation of

Challenges Moving Forward

- Continue placebo-controlled trials or (partially) cross-over from placebo to…
  - … trial vaccine
  - … other vaccine

  } ‘EUA’ + recommendation for use (in risk groups) + supplies available at country level
- Correlates of Protection (CoP)
  - Breakthrough cases
  - Standardised assays allowing comparability across programmes / platforms
- Evidence on infection / transmission
- Heterologous prime-boost
- Clinical trial sites
- (Long-term) vaccine safety
  - Pre-licensure
  - Post-licensure
- Long COVID
- …

Manufacturing / supply: cold chain, 2-dose regimen: different formulations for 1st / 2nd dose, …

Placebo groups: Continue or Cross-over?

- Continue placebo groups for as long as possible
  - SWAT Workshop, Oct 28th
  - WHO consultation, Nov 6th → position paper published 2nd December
- Some developers may choose to cross-over quickly …
  - … in countries where EUA has been obtained
  - … specific risk (=trial) populations with a public health recommendation to get vaccinated (HCW, elderly, underlying medical conditions, …)

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Placebo-Controlled Trials of Covid-19 Vaccines — Why We Still Need Them

WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation

Recent announcements that some Covid-19 vaccines are estimated to have high short-term efficacy provide new hope that vaccination will soon contribute to controlling the pandemic.

The initial roll-out of limited quantities of vaccines that are still investigational will provide the opportunity to ethically obtain pivotal data to improve regulatory and public health decision making, thereby increasing public and professional confidence in these and other vaccines.

After relatively short follow-up posure to SARS-CoV-2, information on protection against clinically severe forms of Covid-19, and knowledge of any associations between the degree of protection and the recipient's age or coexisting conditions. Even after the first vaccines become available, it will still be important to evaluate additional vaccines to while it is still feasible and ethical, ongoing studies and others that are about to start should continue to collect high-quality information using directly randomized comparisons against placebo to address as many of the data requirements as possible. While vaccine supplies are limited, available vaccines are still investigational, or public health recommendations to use those vaccines have not been made, we believe it is ethically appropriate to continue blinded follow-up of placebo recipients in existing trials and to randomly

The members of the WHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation (Philip R. Krause, M.D., Thomas R. Fleming, Ph.D., Ira M. Longini, Ph.D., Richard Peto, F.R.S., Valerie Beral, F.R.S., Balram Bhargava, M.D., Alejandro Cravioto, Ph.D., Jakob P. Cramer, M.D., Susan S. Ellenberg, Ph.D., J. Peter Figueroa, Ph.D., Elizabeth Halloran, Ph.D., Ana M. Henao-Restrepo, M.D., Michael J. Ryan, M.D., Myron M. Levine, Ph.D., Martha Nason, Ph.D., Hanna M. Nohynek, Ph.D., Stanley Plotkin, Ph.D., Helen Rees, Ph.D., Jerome A. Singh, Ph.D., and Soumya Swaminathan, M.D.) assume responsibility for the overall content and integrity of this article.

Placebo groups: Continue or Cross-over?

Points to consider:

- Ethical / regulatory aspects
- Vaccine-related safety events usually occur within 2-3 months post vaccination
- Unrealistic to maintain placebo-group for 12 or even 24 months anyway
- Rapid and complete cross-over would …
  - … facilitate conduct of the trial / data analysis
  - … simplify maintaining the blinding
  - … increase the absolute number of breakthrough cases → accelerate establishment of a CoP

Placebo groups: Continue or Cross-over – next steps

FDA VRBPACs:

- Pfizer / BioNTech → 10th December
- Moderna → 17th December

Ongoing Ph3 trials with pivotal results available

- BioNTech / Pfizer
- Moderna
- Astra Zeneca / Oxford (…)
- Gamaleya (?)

Ph3 data expected soon

- China (Sinovac, Cansino, Sinopharm)

Pivotal Ph3 trials to start in the next few months (possibly before end of 2020)

- Novavax
- CureVac
- Clover
- SP / GSK
- BioE

Ph3 trials to start after spring 2021 (→ alternative trial design / strategy to establish VE / CoP ???)

- Merck (IAVI, Themis)

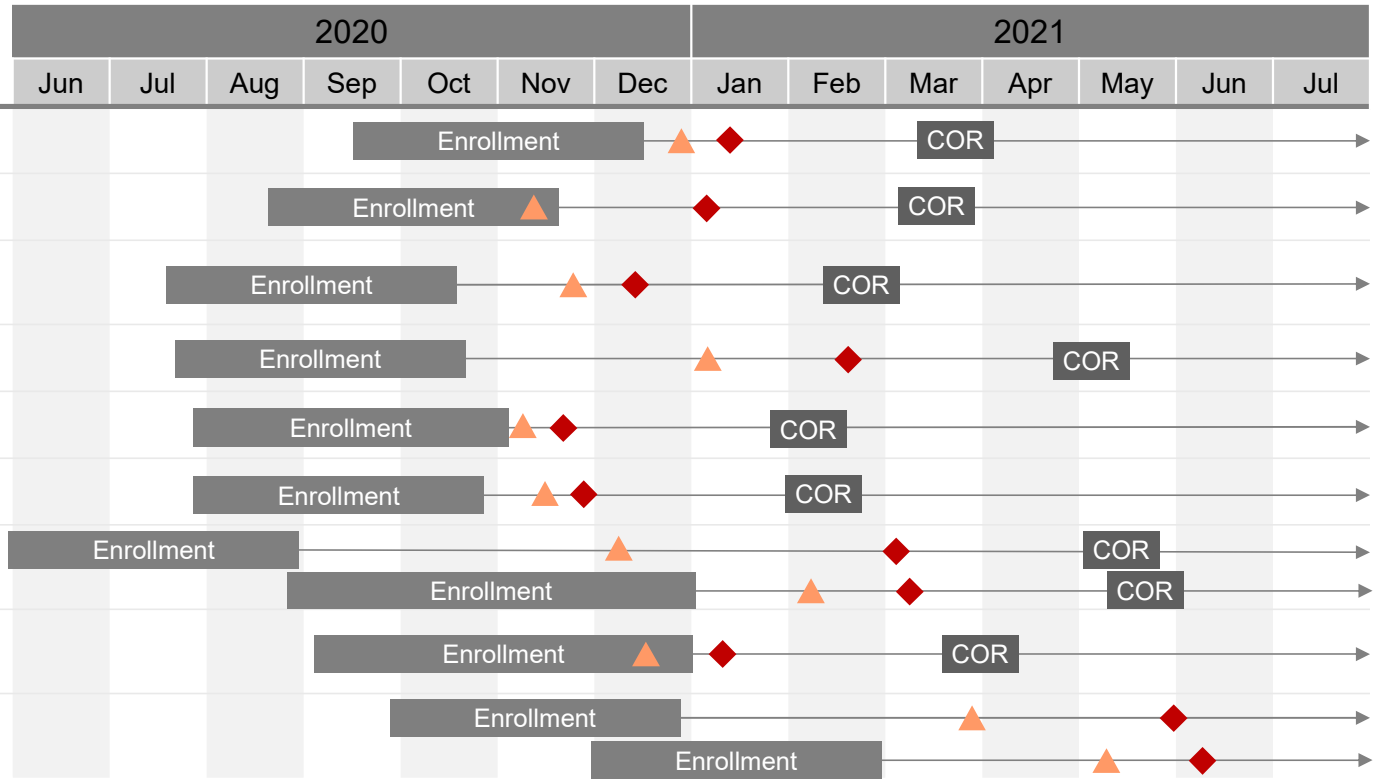
Conclusion and related to correlates of protection: Workshop on Nov 19th

- Strong endorsement of the **neutralizing antibody titer**
  - Bob Seder, Chief, Cellular Immunology Section, Vaccine Research Center (NIH/NIAID): "*It seems like with the number of antibodies you get with vaccines, which often are well in excess of what you get with primary infection, they should be able to protect in the lower airway and potentially in the upper airway for transmission…**the glass is 95% full.***"
- Strong promotion of the **NIBSC / WHO International Standard and Reference Panel for anti-SARS-CoV-2 antibody,** expected to be endorsed in early December
- Analyse efficacy / immune response data across vaccine platform technologies
- Investigate long(er) term immune response in the context of efficacy (and safety)
  - Waning nAbs
  - Memory B-cell
  - …

Landscape and timing of early phase III VE trials that may contribute data to correlates analyses

Key
- Interim analysis
- Primary analysis
- COR — Potential correlates analysis

Developer	Ph III Sites[1]
CanSino	SAU, PAK, RUS
Gamaleya	RUS, BLR, UAE, VEN, IND
Sinopharm	UAE, PER, MAR, ARG, BHR, JOR, EGY
Sinovac	**BRA**, IDN, TUR
Pfizer	**USA**, ARG, BRA, GER, RSA
Moderna	**USA**
Oxford / AZ	BRA, **UK**, IND, RUS **USA**
Janssen	USA, BRA, ARG, CHL, COL, MEX, PER, PHL, RSA, UKR
Novavax	RSA, **UK**, MEX **USA**[2]



Assumptions:
- 6-month attack rate:
  - US, UK: 2%
  - Others: 5%
- VE: 50%
- Interim analysis: 75 cases
- Primary analysis: 150 cases
- Recruitment / vaccination: 3 mo.
- Follow up for VE endpoint: 2 mo.
- Data mgt & analysis before IA and PA: 1 mo.
- Preparation of correlates report: 2 mo.

How might we expedite? COVAX Clinical SWAT exploring options:
- "Real time" analysis: Cases analyzed as they accrue
- Minimize time between primary and correlates analyses
- Pool data within platforms

1. Where developers are conducting multiple Phase III studies, timeline represents site with predicted earliest readout (bolded), based on public sources (primarily clinicaltrials.gov) and modeled assumptions. 2. Actual start date and study design *TBC*.

CEPI Centralized Laboratory Network

CEPI

For more information: centralizedlab@cepi.net

SARS-CoV-2 Infection and Transmission

- Next workshop on December 17th: Pre-/Post-Licensure Assessments of COVID019 Vaccine Efficacy against Infection and Transmission
  - ➢ Data from ongoing (and planned) Ph3 trials re infection / transmission
  - ➢ What are the gaps?

Pre-licensure

Post-licensure

Approaches:

- Pre-clinical data
- Prevention of clinical symptoms facilitating transmission (e.g. cough)
- Vaccine efficacy on asymptomatic infections, either based on
  - Weekly PCR / RDTs (sensitivity? specificity?)
  - (repeated) seroconversion to antigens not included in the vaccine, e.g. N-protein (duration of anti-N post natural infection?)
- Viral shedding in confirmed COVID-19 cases (impact of specimen / sampling technique?)
- Household transmission (sub-studies in participants with confirmed COVID-19)
- Observational studies (cluster-randomized studies, cohort studies

Primary Immunization: Heterologous Prime-Boost

Advantages:

- May improve immune response (titre level, persistence of Ab levels, breadth of the immune response, …)
- Increase manufacturing capacity
- Reduce cost

But:

- Logistical challenge
  - Different storage conditions
  - Different application route / technique
  - What if prime or boost are out of stock?
- Different contraindication for prime-boost?
- Different tolerability profile?
- Errors:
  - Can I give vaccine B and the vaccine A?
  - Can I give vaccine A twice?
  - Can I give vaccine B twice?

Site readiness funding for efficacy studies

The purpose of these investments is to fund PDPs to identify and fund experienced clinical trial sites in LMIC countries to build their readiness for eventual implementation of COVID-19 Phase 3 clinical efficacy trials

Scope of Work

- Three PDPs will identify sites and distribute funds:
- **PATH**
- **International Vaccine Institute**
- **D'Or Institute for Research & Education**

Site Readiness Timeline (sites supported by COVAX delayed by ~2-3 months)

Deadline	Activities
September 30	• Sites assessed and selected for funding
October 31	• Site contracts in place with selected sites
November 15	• Sites funded to address trial readiness gaps • Funded activities include infrastructure expansion, equipment needs, staff time and training, regulatory / ethics preparation, and disease surveillance
December 1	• Site strengthening activities finalized • PDP defines country-specific readiness criteria • Majority of sites ready to begin enrolling subjects for Phase 3 trial
December 30	• Sites assessed as formally ready by independent evaluator

Overview of sites (selected and under current consideration)

As of December 3: 30 sites contracted with BMGF funding; 8 more under consideration with COVAX funding

Site under contract with BMGF funding

Site under consideration with COVAX funding

Map indicates new COVID-19 cases per 100k (7-day avg) as of December 3 from Google Maps, map available here (to see incidence, must be using iOS device)

Vaccine Safety / Pharmacovigilance

- Support the developers' needs encompassing pre-, peri- and post-authorization PV activities within COVAX with IFPMA and DCVMN input
- Support PV integration and capacities considering vaccine allocation post-authorization
- Address concerns:

- Vaccine distribution / procurement pathways and respective PV roles and responsibilities:
  - How to ensure vaccine exposure and legal PV responsibility by product and country, when developers / manufacturers / MAHs do not know which vaccine will be used where, when, by which mechanism.
- PV post-authorization ecosystem – global roles and responsibilities:
  - How to avoid overlaps, duplicates, omissions in PV post-authorization / post-introduction (e.g., active post-licensure activities master protocols for PASS, CEM, sentinel methods etc.)
  - How to allow data sharing, pooling outputs etc.
  - Mapping of existing platforms (HIC vs LMIC)
  - Mapping of updated recommendations and their feasibility (e.g., what data to be collected for which product in which countries / regions etc.)
- Safety signal post-introduction:
  - Need for broader platform, not only including individual groups but also different stakeholders
  - Need for and expert advisory group for developers needs to facilitate and coordinate discussions and safe data sharing
  - Need for transparency, i.e., global overview of safety of all vaccines from different platforms
  - Causality assessment and recommendations for countries, regions, regulatory agencies and developers

Thank you for your attention!!

Email: jakob.cramer@cepi.net

https://epi.tghn.org/covax-overview/