Biological E. Limited

Celebrating Life Every Day

Covid-19
Vaccine activities

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DCVMN AGM

5 Nov 2020

COMMITTED TO PROVIDING ACCESS TO AFFORDABLE HEALTHCARE

Biological E and the Global Vaccine Market

Biological E is one of the leading vaccine manufacturers providing equitable access to quality vaccines to millions of children in the world

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1 out of 5 children in the world is immunized by vaccine made by Biological E*

Biological E supplies 20 % of the world vaccine demand

*Source: WHO MI4A Global Vaccine Report (bOPV volumes excluded)

- We manufacture 2 million doses of vaccine every day
- Supply vaccine to more than 100 countries
- Leading supplier of pentavalent vaccine in the world
- 2016-2018 : Every kid born in India would've received a vaccine made by BE
- Largest manufacturer of TT vaccine

World class Manufacturing facilities

1st private sector biological products company in India

Founded as Biological Products Pvt Limited in 1953, we are the first private sector biological company in India and also the first Indian private company to enter the vaccine market

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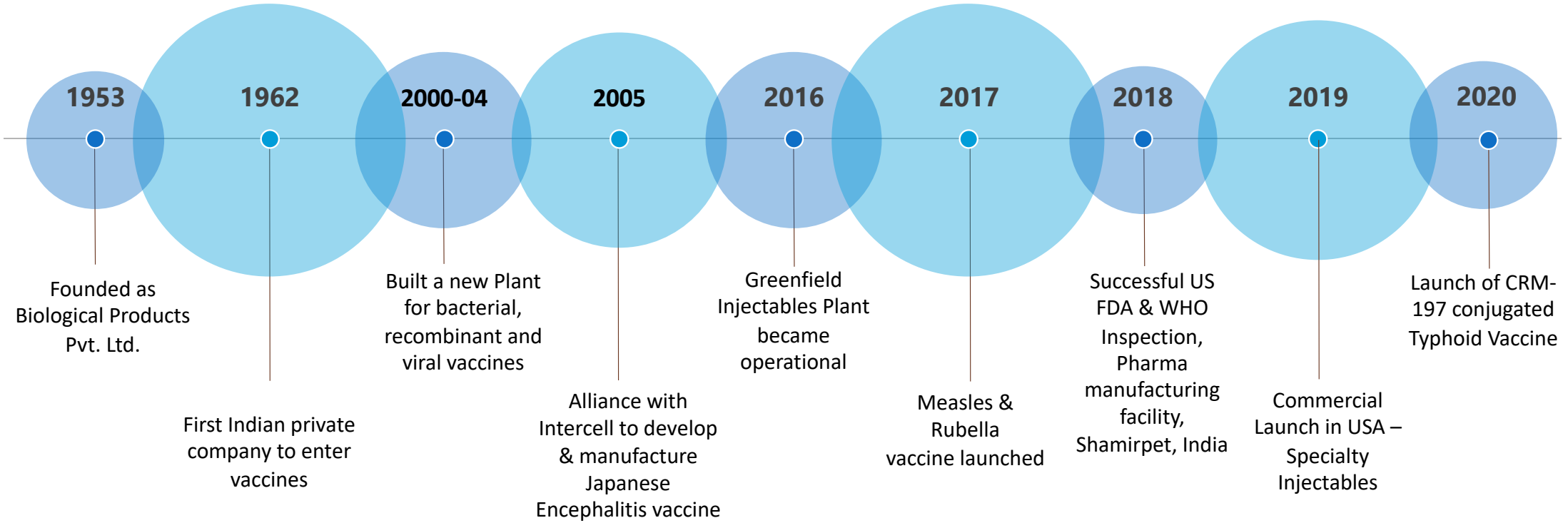
Established in 1953, Biological E. Limited (E) started during a time when the nation sought access to critical healthcare products. BE was founded and led by Dr. DVK Raju, with an objective of transitioning from treating diseases to preventing them. BE launched its Biotechnology Division (now Vaccines and Biologics Division) and commenced large-scale production of DPT vaccines as early as 1962. BE continues to evolve as an organization and currently has four strategic business units: Branded Formulations, Specialty Generic Injectables, Synthetic Biology and Vaccines and Biologics.



Our products and technology platform capabilities

Biological E's WHO pre-qualified vaccines are the backbone of global immunization programs. With a strong pipeline of new generation products, Biological E could soon meet the end to end immunization needs of any country

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WHO Prequalified
- ✓ TT
- ✓ Td
- ✓ Liquid Pentavalent
- ✓ Japanese Encephalitis
- ✓ DPT
- ✓ Measles & Rubella

Currently Under WHO Review for PQ:
- ✓ Typhoid Conjugate vaccine
- ✓ Hepatitis-B

Vaccine under pipeline:
- ✓ PCV
- ✓ IPV
- ✓ Hep A
- ✓ Hexavalent
- ✓ TdaP
- ✓ Covid 19

US FDA Approved

- ✓ 4 products commercialized

Product Pipeline

- ✓ Currently working on a portfolio of ~ 25 products
- ✓ Complex long acting injectables

Infrastructure for Antigen types:
- ✓ Microbial -Recombinant & native strains (Bacterial, Yeast)
- ✓ Mammalian cell culture based (Live virus, Inactivated virus, Proteins)
- ✓ Conjugate vaccines

Fill Finish infrastructure for:
- ✓ Blending suites
- ✓ Lyophilized Product
- ✓ Liquid Vial Product
- ✓ Pre-Filled Syringe Product

Product testing infrastructure for:
- ✓ Animal testing
- ✓ Virology, Biochemical testing
- ✓ Microbiology


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Covid-19

Activities to combat COVID-19 disease

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Biological E COVID-19 projects

1. Bio E signed an agreement with Johnson & Johnson (J&J) unit Janssen Pharmaceutica to manufacture J&J's Covid-19 vaccine candidate, Ad26.COV2.S, currently in Phase III clinical trial
   - deploying its manufacturing infrastructure to support Johnson & Johnson's commitment to global access for its Covid-19 vaccine and increase production capacities by annually 500 mds for drug substance and drug product
   - supporting J & J' s commitment to global access for its Covid-19 vaccine

2. Bio E is partnering with Baylor College of Medicine (BCM), Texas to develop and commercialize a Covid-19 vaccine candidate
   - received a licence to the recombinant protein RBD
   - using Bio E's recombinant Pichia pastoris expression platform and infrastructure; project is currently entering Phase I / II clinical trial
   - in line with Bio E's vision to make vaccines affordable and accessible to all

3. BioE has tied up with NIV-Pune-ICMR to develop equine anti-SARS-CoV-2 immunoglobulin product
   - employing Bio E's process platform to achieve effective immunization of horses with inactivated virus, supplied by NIV
   - employing Bio E's process platform to produce highly purified equine immunoglobulin F(ab')2 product based on enzymatic processing of hyper-immune plasma
   - project is currently entering Phase I / II clinical trial to treat hospitalized COVID-19 patients with moderate disease symptoms

COVID-19 Vaccine,
Product concept: Receptor binding protein (RBD)

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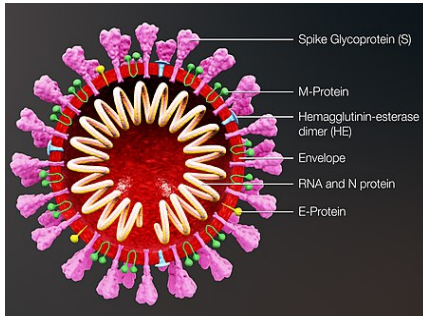
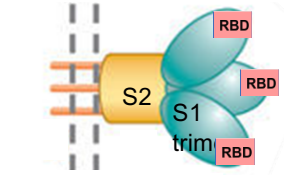
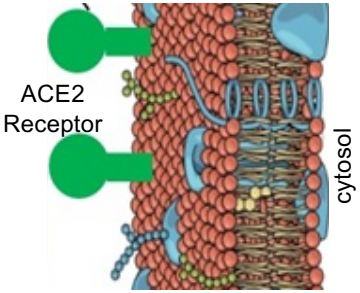
Virus and infection mechanism:

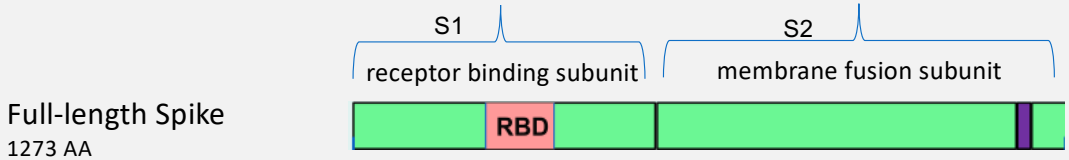




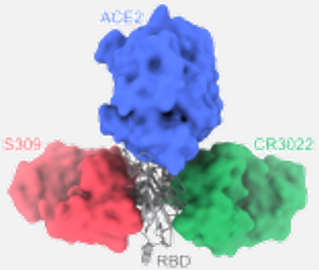
infection



Vaccine candidates: *Protein; adjuvanted*



Mechanism of vaccine action:
Antibodies against RBD prevent binding to hACE2 receptor: **affecting infection and disease severity**



CR3022: not a neutralizing antibody
hACE2 and S309: neutralizing anitibodies

Activities to combat COVID-19
RBD vaccine candidate

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Goal:

- develop a vaccine against COVID-19 based on an antigen derived from Receptor Binding Domain (RBD) of Spike (S) Protein of SARS-CoV-2 surface, with demonstrated safety, immunogenicity and efficacy
- Bio E's rationale to develop a RBD based vaccine candidate
  - A scientifically promising vaccine approach
  - Classical proven vaccine manufacturing technology

  in combination with Bio E's existing capabilities
  - process and manufacturing infrastructure plus knowledge to develop a vaccine fast and reliably
    - process / analytical development, GMP manufacturing in Pilot plant, in-house pre-clinical Toxicology study capability, clinical and Regulatory experience
  - large scale process platform Pichia *pastoris* (product Hep B)
  - large-scale facilities with bioreactors (3500 L scale, re-purposed) for Drug Substance
  - large-scale facilities for Drug Product (blending and filling)

=> Resulting in affordable and large-scale vaccine quantities

Activities to combat COVID-19
RBD vaccine candidate

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TPP

S. No.	Considerations	Desirable Criteria
1	**Market**	Global Health
2	**Presentation**	Vials (1, 2, 5, 10, 45 ds/vial) and PFS
3	**Administration regimen**	1-2 dose
4	**Shelf Life**	≥ 2 years
5	**Cumulative heat exposure**	VVM14 or higher
6	**Formulation**	Liquid
7	**Vaccine components/dose**	One defined antigen
	Antigen	RBD
	Adjuvant	Alum plus CpG (Th1/Th2 balanced)
	Preservative	No preservative, open vial policy *(Thiomersal / 2-Phenoxyethanol: later)*
	Other excipients	GRAS buffer systems
	Final pH	6.5 – 7.5

TPP developed for a vaccine candidate based on classical vaccine technology (and inline with WHO TPP)

- a recombinant protein antigen (RBD of S1-subunit of S-protein)
- in combination with a
  - commercially available adjuvant Alhydrogel (Alum/AH)
  - known Th1 skewing TLR 9 immunomodulator: CpG

Rationale for selecting Alum / CpG as adjuvant system:

- RBD antigen + Alum / CpG: resulting in a stable formulation
- fits well within Bio E's technical expertise (Production & Quality Control) of commercially manufactured vaccines
- staff experience / training, technical infrastructure for formulation, filling lines, multi- & single dose vial inspections
- part of Bio E's routine manufacturing handling vaccine suspensions

Activities to combat COVID-19
RBD vaccine candidate

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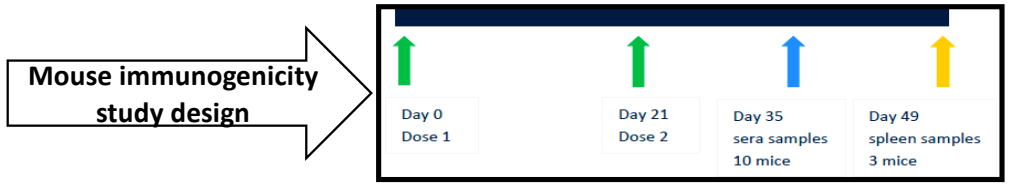
- RBD antigen construct (RBD219-N1-C1 or N1C1) in *P. pastoris*
  - received from laboratory of Prof. Peter Hotez at the Baylor College of Medicine (BCM), USA
  - high productivity
  - adjuvant compatibility: Alum / CpG
- Pre-clinical PoC trials – immunogenicity studies in mouse model:
  - animal model: Balb/C mouse (female; 13 animals/cohort)
  - route of administration: intramuscular (i.m.)
  - dosage: 100 mL / dose (2-dose regimen)
  - treatment arms:
    6 formulations (varying combinations of RBD-N1C1, and Alum (AH) / CpG)



Samples evaluated for:
- Binding antibody and RBD-ACE2 binding inhibition titers
- Neutralizing antibody titers
  - Pseudo(-typed) virus
  - Wild-type virus
- Th1/Th2 response
  - End-point titers of IgG1, IgG2a, IgG2b
  - Cytokine Expression

Activities to combat COVID-19
RBD vaccine candidate

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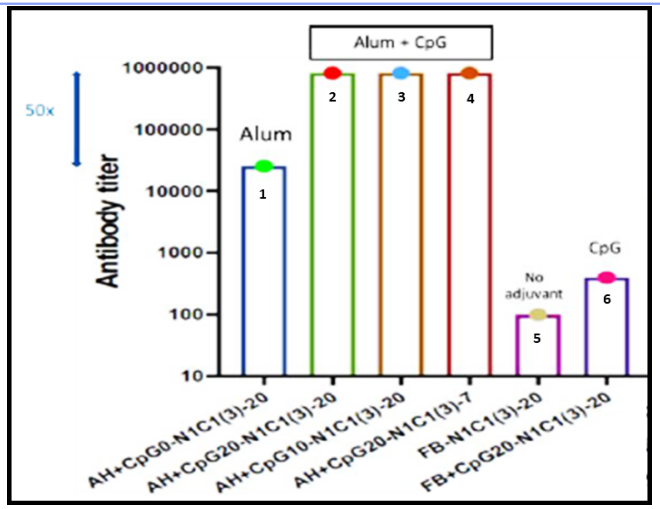
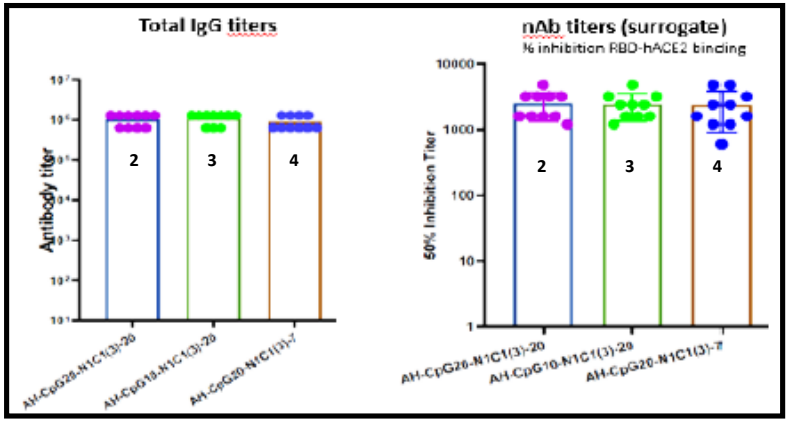
- **Binding antibody titers (IgG, ELISA)**
  - total IgG titer: determined by ELISA method
    - plate coated with RBD-N1C1
  - RBD w/o adjuvant:
    - poorly immunogenic (bar 5)
  - AH & CpG added separately:
    - increased IgG titers (bars 1, 6 respectively)
  - *AH+CpG (bars 2, 3, 4):*
    - ***50x** higher IgG titers than AH alone titers* (bar 1)
  - RBD 20 µg (bar 2) vs 7 µg RBD (bar 4): *IgG saturation*



- **Binding inhibition titers (ELISA)**
  - inhibition of RBD binding to hACE2 receptor by sera
  - high inhibition = high neutralizing antibody (nAb) titer
  - seroconversion of all animals
  - *showed a similar antibody titer pattern as total IgG titers (bars 2, 3, 4)*



Activities to combat COVID-19
RBD vaccine candidate

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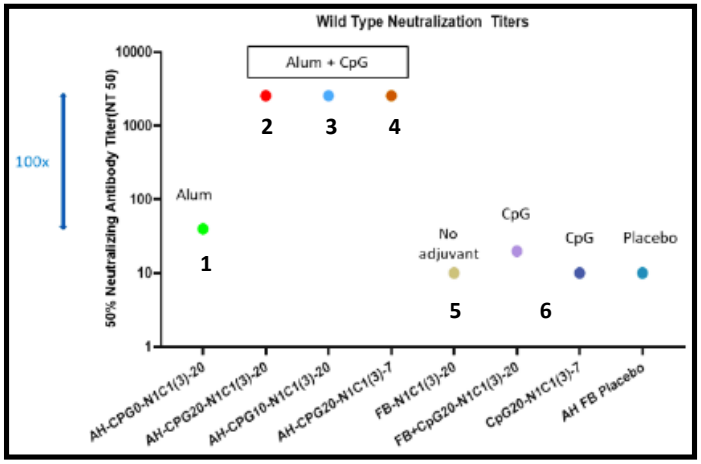
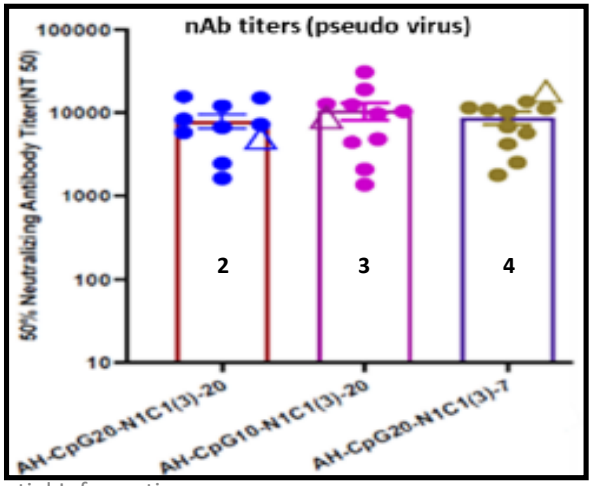
- **Wild-type virus neutralization assay (SNT):**
  - Sera nAbs binding / neutralizing SARS-CoV-2 virus, reduce plaque formation of infected of Vero 6 cells:
    high serum dilution number (@50% CPE inhibition) = high nAb titer (NT50):
    most reliable parameter for antibody titer
  - performed at Translational Health Science and Technology Institute (THSTI), India
  - *AH+CpG (dots 2, 3, 4):*
    *- **100x** higher IgG titers than AH alone* (dot 1)



- **Pseudo(-typed) virus neutralization assay (PNA):**
  - Sera nAbs binding to non-replicating lentiviral particle (SARS-CoV-2 Spike protein) reduce the luciferase signal of infected human hACE2-293T cells:
    high serum dilution number (50% signal inhibition) = high nAb titer (NT50):
    - surrogate parameter for antibody titer
  - performed at Nexelis, Canada
  - seroconversion of all animals at high titer



- Adjuvant system Alum (AH)+CpG: identified as the most favourable for RBD-N1C1 vaccine candidate

COVID-19 Vaccine : Clinical Plan Overview

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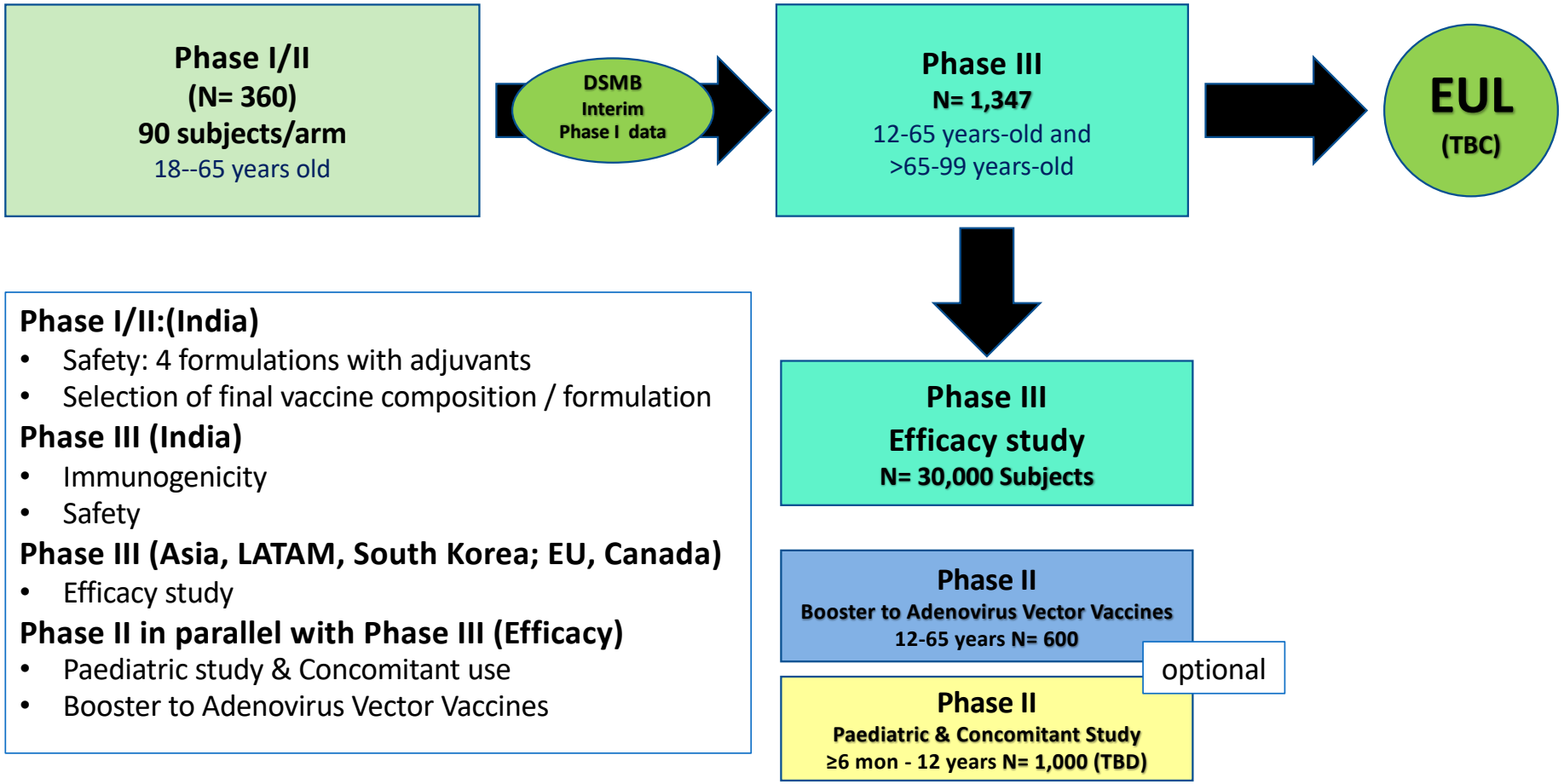

Phase I/II:(India)
- Safety: 4 formulations with adjuvants
- Selection of final vaccine composition / formulation

Phase III (India)
- Immunogenicity
- Safety

Phase III (Asia, LATAM, South Korea; EU, Canada)
- Efficacy study

Phase II in parallel with Phase III (Efficacy)
- Paediatric study & Concomitant use
- Booster to Adenovirus Vector Vaccines

Development Timelines

Vaccine candidate is entering Phase I clinical trials in Nov 2020 and is expected to be licensed by October 2021

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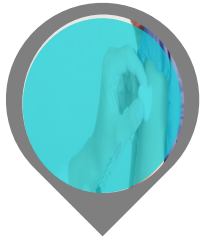
Sep 2020

Pre-clinical trial completion

Mar 2021

Phase I / II Clinical trial completion

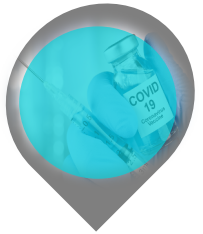
Jun 2021



Phase III Clinical trial (Safety / immunogenicity) completion

Sep 2021

Phase III Clinical trial
Efficacy
- Interim read-out



Commercial Licensure

Oct 2021

Expected Commercial Availability

Oct'21


COMMITTED TO
PROVIDING
ACCESS TO
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THANK
YOU
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