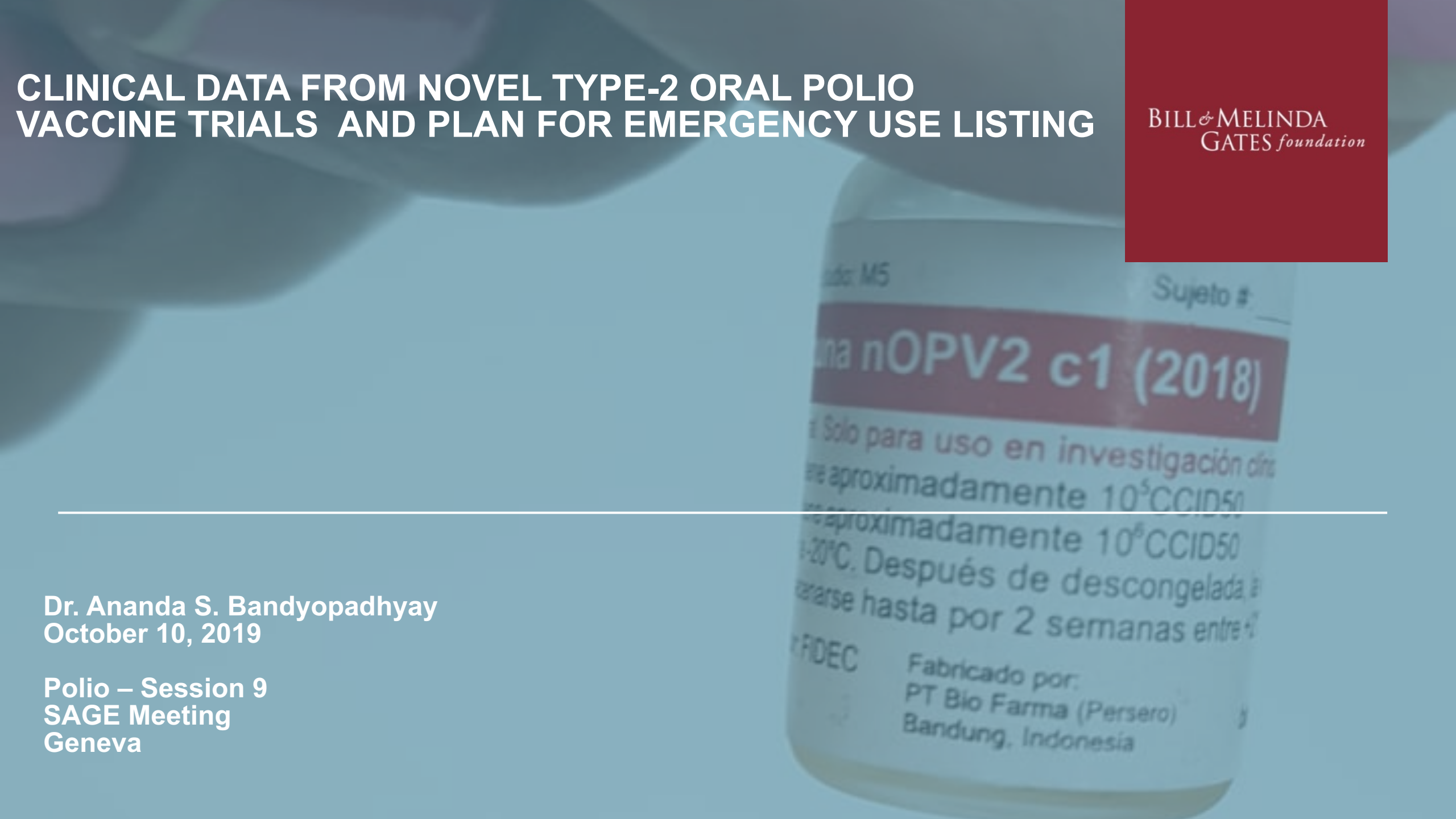
CLINICAL DATA FROM NOVEL TYPE-2 ORAL POLIO VACCINE TRIALS AND PLAN FOR EMERGENCY USE LISTING

BILL & MELINDA GATES foundation



Dr. Ananda S. Bandyopadhyay
October 10, 2019

Polio – Session 9
SAGE Meeting
Geneva

OUTLINE

- Background
- Clinical Development Plan
- Data from Phase I, II Studies
- Plan for EUL
- Manufacturing and Supply Estimates
- Next Steps

NOVEL OPV-2 DEVELOPMENT: BACKGROUND

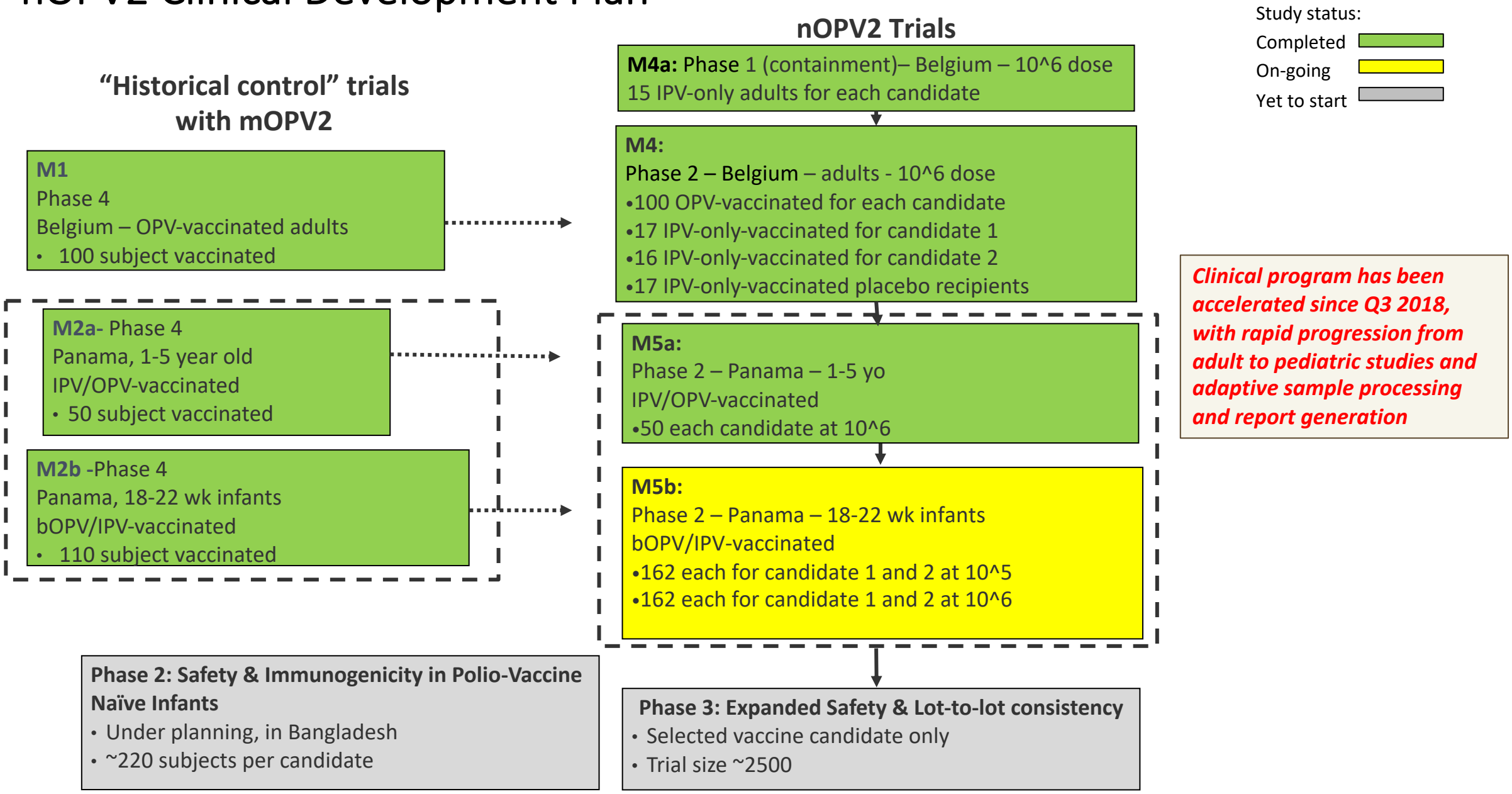
Objective:

To reduce the risk of vaccine associated paralytic poliomyelitis (**VAPP**) and circulating vaccine derived polioviruses (**cVDPV**) when deployed in response to a type 2 cVDPV outbreak occurring after global discontinuation of OPV2.

Status:

- Two nOPV2 candidates designed to improve **genetic stability** and decrease the risk of loss of attenuation relative to the parental Sabin 2 strain: pre-clinical data supportive of further development
- Human **clinical** trials initiated in **2017**. Phase I study in **Antwerp** (under containment) completed, and results published.
- Phase II: in adults in **Antwerp** and **Ghent** completed in Q2 2019.
- Phase II: in toddlers/infants in **Panama** completed in Q3 2019 for key field-activities, long-term safety follow up pending.
- **One candidate** provisionally **prioritized** for manufacturing-at-risk given global public health emergency and program need.

nOPV2 Clinical Development Plan



Clinical program has been accelerated since Q3 2018, with rapid progression from adult to pediatric studies and adaptive sample processing and report generation

NOVEL OPV2 DEVELOPMENT: FIRST-IN-HUMAN STUDY

Pierre Van Damme, Ilse De Coster, Ananda S Bandyopadhyay, Leen Suykens, Patrick Rudelsheim, Pieter Neels, M Steven Oberste, William C Weldon, Ralf Clemens, and Hilde Revets. **Poliopolis**: pushing boundaries of scientific innovations for disease eradication. ***Future Microbiology***. 2019.

FIRST-IN-HUMAN STUDY: OUTCOME AT A GLANCE

- Generally safe and well tolerated; no serious adverse events
- Clear evidence of replication in gut (15/15 and 13/15 fecal shedding positive for candidate 1 and 2, respectively)
- Clear evidence of immunogenicity (rise in serum neutralizing antibodies)
- Shed virus had no meaningful increase in neurovirulence compared to administered candidates
- Deep sequencing data consistent with expectations; no changes in domain V that are anticipated to increase virulence detected.

Van Damme, P., De Coster, I., Bandyopadhyay, A. S., Revets, H., Withanage, K., De Smedt, P., ... & Clemens, R. (2019). The safety and immunogenicity of two novel live attenuated monovalent (serotype 2) oral poliovirus vaccines in healthy adults: a double-blind, single-centre phase 1 study. ***The Lancet.*** **2019.**

PRELIMINARY TAKEAWAYS FROM PHASE II STUDIES (BELGIUM, PANAMA)

Data and Safety Monitoring Board (DSMB) actively engaged in regular review of general safety data from clinical studies, and has supported progression across adults – toddlers – infants cohorts, and use of high-low dose of candidates based on favorable assessment of **general safety** information so far.

Both candidates appear to be **immunogenic**

- In OPV immunized **adults** (2016 C1 and C2; 10^6 $CCID_{50}$):
  - One dose seroconversion rates for both C1 (~75%) and C2 (~51%) exceed those for Sabin 2 (~29%; ≥10^5 $CCID_{50}$)
  - Point estimates tend to favor candidate 1 over candidate 2
- In OPV – IPV immunized **toddlers** (2018 C1 and C2; 10^6 $CCID_{50}$):
  - One dose seroconversion rates (~95%) for both C1 and C2 exceed those for Sabin 2 (~63%; ≥10^5 $CCID_{50}$) (History of multiple tOPVs in historic control subjects, predominantly bOPV-IPV in C1/C2 subjects)
- In bOPV - IPV immunized **infants** (2016 C2):
  - At low dose (≈10^5 $CCID_{50}$): One dose seroconversion = 73%
  - At high dose (≈10^6 $CCID_{50}$): One dose seroconversion = 93%

PRELIMINARY TAKEAWAYS FROM PHASE II STUDIES (BELGIUM, PANAMA)

Both candidates **replicate** in human gut

- Overall pattern of shedding (prevalence, duration, titer) similar to mOPV2 observations
- Estimates indicate greater extent and duration of shedding for C1 vs. C2

Both candidates demonstrate evidence of **genetic stability**

- No domain V (primary attenuation site) reversion detected in any samples of either candidates in M4 study in adults
- Other variants appear consistent with observations from first-in-human study

Caveats

- All data from adults and toddlers are with the HD ($\approx 10^6$ $CCID_{50}$) formulation for candidate vaccine lots compared to $\geq 10^5$ $CCID_{50}$ of mOPV2
- Limited comparative value with historic controls due to variance in population dynamics, prior polio vaccination status (etc.)

PLAN FOR ACCELERATED EUL SUBMISSION

Objective:

- Attain alignment with WHO PQ and BPOM on a streamlined dossier and filing strategy. This will enable the earliest possible EUL submission, review and decision-making in Q1-Q2 2020, including agreement that new data can be submitted either during review or following approval of the EUL.

Approach:

- The proposed EUL dossier is to include non-clinical research data, CMC data on nOPV2 product supplied from a pilot facility, clinical safety and immunogenicity data in adults, toddlers and infants, as well Next Generation Sequencing (NGS) and neurovirulence (NV) data from vaccine virus shed from adults and toddlers.
- Subsequent submissions will be made to support the supply of nOPV2 from commercial scale facilities and will include NGS and NV assessments of vaccine virus shed from infant cohorts.
- Support for Phase III studies, PQ/licensure will be continued for longer term use of the vaccine.
- Additional data can be generated through pharmacovigilance including through the extensive network of global polio surveillance.

EUL SUBMISSION PROPOSAL & TIMELINE

*Initial submission, expected to enable EUL approval for first use of nOPV2

Clinical Dataset		February 2020	March 2020	September 2020	March 2021
Clinical Overview		Initial Submission*		Updates	
M4a	Phase 1 adults	X			
M4/ M1	Safety, serology, shedding, post dose 1 DS/NV	X			
	Final NV analysis				X
M5/ M2	Safety through day 28 post-last-dose	X			
	Serology & toddler shedding	X			
	M2 and M5 Toddler post dose 1 DS/NV		X		
	M2 and M5 high dose, post first dose, infant cohort viral shedding			X	
	M5 low dose, post dose 1, infant cohort viral shedding				X
	M2 and M5 high dose, post dose 1, infant cohort, deep sequencing and neurovirulence			X	
	Final NV analysis				X
	Six-month safety follow up			X	
	Final M5 CSR				X

Other Content	February 2020	July 2020
Clinical Study Reports and Key Sections of the Common Technical Document (CTD) -- Administrative/Regional, Summaries (Introduction, Quality Overall Summary, Non-Clinical Summary) and Quality (CMC)	Initial Submission*	
Updated Sections of the CTD – Quality Overall Summary and Quality (CMC) -- for commercial-scale facility		Subsequent Submission

MANUFACTURING AND SUPPLY: ESTIMATES FOR NEAR-TERM

FACILITIES / SCALE	PLANNED EUL SUBMISSION	DETAILS
Pilot	February 2020	Release 3 Bulk DS* and 3 DP** lots Produce 10 additional DS lots
Commercial	June/July 2020	Produce 6-7 DS lots Assume fill all in 20 doses /vial
Foundation funded stockpile plan in support of EUL		~100M filled doses by ~Q2 2020

ASSUMPTIONS	RISKS TO ACHIEVING FILLED DOSE TARGET
• Yield Estimates with current titer • 20 doses/vial. Currently assessing stability and suitability of ~50 doses/vial	• Actual yields lower than forecast from titer of the first 3 lots • Unable to scale up from pilot to commercial scale • Start up of commercial facilities takes longer than projected • Not all lots end up being releasable (currently assuming 100% success rate) • Fill/Finish losses greater than current estimates

*Drug Substance **Drug Product

ISSUES FOR FOLLOW-UP

Recommendations under EUL

- Will recommended use of nOPV2 differ in any way from current mOPV2 use?

Prioritization of limited supplies

- Use of nOPV2 *and* mOPV2 for near-term

Plan for initial field-use of nOPV2 and "cessation" of mOPV2

- Prioritization of geography, scope, communications

Plan and implement additional studies for supportive data

- Study in polio vaccine naïve infants; others under consideration


cevaxin
NO
DESCONECTAR
cevaxin
centro de vacunación internacional

THANK YOU .. !

APPENDIX

M4 (BELGIUM) STUDY: IMMUNOGENICITY RESULTS FROM OPV-COHORT

			Study M4 (nOPV2)		Study M1 (Sabin mOPV2)
			C1, 10^6 $CCID_{50}$ (N=100)	**C2, 10^6 $CCID_{50}$ (N=100)**	**≥10^5 $CCID_{50}$ (N=100)**
Post-dose-1	Seroprotected	n/N (%)	96/96 (100)	98/98 (100)	98/100 (98.0)
		LCI, UCI	96.2, 100	96.3, 100	93.0, 99.8
	Seroconversion*	n/N (%)	**41/55 (74.5)**	**24/47 (51.1)**	**18/62 (29.0)**
		LCI, UCI	61.0, 85.3	36.1, 65.9	18.2, 41.9
	Serum NAbs	GMT CI	3904 1907, 7994	1096 756.3, 1588	707.3 439.1, 1139
Post-dose-2	Seroprotected	n/N (%)	49/49 (100)	49/49 (100)	49/50 (98.0)
		LCI, UCI	92.7, 100	92.7, 100	89.4, 99.9
	Seroconversion*	n/N (%)	**20/27 (74.1)**	**15/26 (57.7)**	**11/29 (37.9)**
		LCI, UCI	53.7, 88.9	36.9, 76.6	20.7, 57.7
	Serum NAbs	GMT CI	5921 1694, 20698	1401 805, 2437	957.2 452.6, 2024

*Subset of subjects with baseline immunity (NAb titer) sufficiently low to enable observation of seroconversion (≤8.5 log2).

PRELIMINARY, SUBJECT TO CHANGE – COURTESY UNIVERSITY OF ANTWERP

M5 (PANAMA) STUDY: IMMUNOGENICITY FROM 2018 TODDLER COHORT

			C1, 10^6 $CCID_{50}$ (N=49)	C2, 10^6 $CCID_{50}$ (N=51)	M2, $\geq 10^5$ $CCID_{50}$ (N=50)
Post-dose-1	Seroprotected	n/N (%)	39/39 (100)	47/47 (100)	46/46 (100)
		LCI, UCI	91.0, 100	92.5, 100	92.3, 100
	Seroconverted*	n/N (%)	17/18 (94.4)	23/24 (95.8)	5/8 (62.5)
		LCI, UCI	72.7, 99.9	78.9, 99.9	24.5, 91.5
Post-Dose-2	Seroprotected	n/N (%)	39/39 (100)	46/46 (100)	46/46 (100)
		LCI, UCI	91.0, 100	92.3, 100	92.3, 100
	Seroconverted*	n/N (%)	18/18 (100)	22/23 (95.7)	5/8 (62.5)
		LCI, UCI	81.5, 100	78.1, 99.9	24.5, 91.5

PRELIMINARY, SUBJECT TO CHANGE– COURTESY FIDEC

*SC computed among those with SC possible to observe (sufficiently lower than assay ULOQ to enable observation)
Note: fold-rise poorly estimated due to proximity to assay ULOQ

IMMUNOGENICITY RESULTS IN INFANTS FROM CANDIDATE 2, 2016 LOT*

		Low Dose (10^5) Infants [2016 lot] (N=155)	High Dose (10^6) Infants [2016 lot] (N=144)
Day 28	Seroprevalence	125/145 (86.2%)	132/136 (97.1%)
	Seroconversion	100/137 (73.0%)	124/133 (93.2%)
Day 56 (for those receiving a 2nd dose)	Seroprevalence	44/44 (100%)	46/47 (97.9%)
	Seroconversion	40/42 (95.2%)	43/45 (95.6%)

PRELIMINARY, SUBJECT TO CHANGE – COURTESY FIDEC